

SYNOPSIS

Name of Sponsor Company: Eli Lilly and Company Name of Finished Product: Exenatide Injection Name of Active Ingredient: Synthetic Exendin-4	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Protocol No: 2993-117		
Title of Study: An Open-Label Study to Examine the Long-Term Effect on Glucose Control (HbA _{1c}) and Safety of AC2993 Given Two Times a Day to Subjects with Type 2 Diabetes Treated with Metformin, a Sulfonylurea, or Metformin and Sulfonylurea Combination (Phase 3)		
Investigators and Study Centers: Multicenter (3 study centers in Hungary)		
Studied Period: 21 August 2002 through 29 September 2005		Phase of Development: 3
Objectives: Primary Objectives were to assess the effects of subcutaneously injected exenatide administered two times a day in subjects with type 2 diabetes treated with metformin, a sulfonylurea, or metformin/sulfonylurea combination on 1) glycemic control as measured by HbA _{1c} , and 2) long term safety. Secondary Objectives were to examine the long-term effects of subcutaneously injected exenatide administered BID in subjects with type 2 diabetes treated with metformin, a sulfonylurea, or metformin/sulfonylurea combination on fasting concentrations of plasma glucose, fasting concentrations of lipids, body weight, and appearance of anti-exenatide antibodies.		
Methodology: The study was designed with a 4-week initiation period during which all subjects received subcutaneous (SC) exenatide 5 µg BID to minimize the incidence of nausea during the subsequent open-ended maintenance period in which subjects received SC exenatide 10 µg BID. Subjects continued to receive their current dosage of metformin and/or sulfonylurea. At each visit to the clinic, evaluations were performed to assess efficacy, pharmacodynamics, and safety according to protocol objectives. The last measurement collected on or prior to Day 1 before the first injection of study medication was considered as baseline. Three different completer populations were defined based on the length of exenatide exposure: Week 52 completers, Week 100 completers, and Week 132 completers. Based on the statistical analysis plan, efficacy analyses were performed on the Intent-to-Treat (ITT) and all three completer populations; safety analyses were performed on the ITT Population.		
Number of Subjects: The ITT Population comprised 155 subjects who enrolled in the study and received at least one dose of study medication. Within the ITT Population, there were 133 completers at Week 52, 111 completers at Week 100, and 103 completers at Week 132.		
Key Demographics: In the ITT Population, the majority of subjects were female (56.1%), all subjects were Caucasian, the mean age was 58.7 years, and the duration of diabetes was 9.1 years. Mean body weight was 88.8 kg, and the mean body mass index (BMI) was 31.9 kg/m ² . Mean HbA _{1c} was 8.7% and mean fasting plasma glucose concentration was 214.9 mg/dL, indicative of subjects with suboptimal glycemic control. At baseline, 14.8% of subjects were receiving metformin alone, 26.5% of subjects were receiving a sulfonylurea alone, and 58.7% of subjects were receiving a combination of metformin/sulfonylurea.		
Diagnosis and Main Criteria for Inclusion: The study population consisted of subjects with type 2 diabetes treated for at least 3 months with metformin, a sulfonylurea, or a metformin/sulfonylurea combination, and were otherwise healthy and ambulatory. Subjects were 20 to 75 years of age; were male or if female, were either postmenopausal, surgically sterile, or using appropriate contraceptive methods. Eligible subjects were to have an HbA _{1c} of 7.5% to 12.0% at screening; fasting plasma glucose measurement of <280 mg/dL (15.5 mmol/L); a stable body weight not varying by >10% for at least 3 months prior to screening; and BMI of 25 kg/m ² to 45 kg/m ² at screening.		
Test Product, Dose and Mode of Administration: Exenatide 0.25 mg/mL; 5 µg (0.02 mL) and 10 µg (0.04 mL) SC injection, BID.		
Duration of Treatment: 4 weeks initiation, open-ended maintenance.		

Criteria for Evaluation: Efficacy: The primary efficacy endpoints, based on the statistical analysis plan, were the change in HbA_{1c} from baseline to Week 52, Week 100, and Week 132. Pharmacodynamics: Fasting plasma glucose, fasting lipid concentrations, and body weight were assessed for all subjects at each specified visit from screening through the duration of the study. Safety: Safety was assessed by examination of data for adverse events, physical examination findings, clinical laboratory measurements, vital signs, 12-lead electrocardiograms (ECGs), and anti-exenatide antibodies.

Statistical Methods: Efficacy: Efficacy data were summarized for subjects in the ITT Population and in the Completer Populations using observed data. Descriptive statistics were presented both for actual values of, and changes from baseline in, HbA_{1c}, body weight, and fasting plasma glucose and lipid concentrations at each visit. Changes in HbA_{1c} were also summarized by treatment-emergent anti-exenatide antibody titer. Safety: Safety data were summarized for subjects in the ITT Population. Treatment-emergent adverse events (TEAE) were summarized by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA version 6.1), and by intensity. Descriptive statistics for actual values of, and changes from baseline by visit, were calculated for hematology, chemistry, and urinalysis data. ECG and vital signs data were summarized and compared with baseline measurements, and physical examination data were assessed. The incidence of anti-exenatide antibodies was summarized by titer and visit. Safety and efficacy data were analyzed for differences in anti-exenatide antibody-positive versus anti-exenatide antibody-negative subjects.

Efficacy and Pharmacodynamic Results: The following results were observed for the ITT Population (N = 155). Similar results were observed for the Week 132 Completer Population (N = 103). HbA_{1c}: At Week 132, the mean HbA_{1c} was 7.4%, a decrease from a baseline value of 8.6%. The mean changes from baseline in HbA_{1c} were -1.3% at Week 52, -1.0% at Week 100, and -1.0% at Week 132. Reductions from baseline in mean HbA_{1c} values were apparent as early as Week 2 and were observed for the remainder of the study. Fasting Plasma Glucose: At Week 132, the mean fasting plasma glucose was 179.7 mg/dL, a decrease from a baseline value of 214.9 mg/dL. Fasting plasma glucose concentrations decreased rapidly upon initiation of therapy (mean reduction from baseline to Week 2 was 30.1 mg/dL) and were generally sustained throughout the study. The mean changes from baseline for fasting plasma glucose were -31.8 mg/dL at Week 52, -36.4 mg/dL at Week 100, and -33.9 mg/dL at Week 132. Fasting Lipids: Improvements in fasting lipids were observed after increasing exposure to exenatide; the improvements were most pronounced after 132 weeks of treatment. The mean changes from baseline were 5.8 mg/dL for HDL-cholesterol, -10.1 mg/dL for LDL-cholesterol, -14.5 mg/dL for total cholesterol, and -37.7 mg/dL for triglycerides. Body Weight: Reductions from baseline in body weight were maintained through Week 132; the mean body weight decreased to 85.7 kg from a baseline of 88.8 kg. The mean reductions from baseline in body weight were -3.3 kg at Week 52, -3.3 kg at Week 100, and -3.9 kg at Week 132.

Safety: Safety results are summarized for the ITT Population. Adverse Events: The most frequent TEAEs were nausea (42 subjects, 27.1%), hypoglycemia (37 subjects, 23.9%), vomiting (21 subjects, 13.5%), hypertension (16 subjects, 10.3%), and diarrhea (nine subjects, 5.8%). The majority of TEAEs were considered mild to moderate in intensity; 27 events occurring in 21 subjects (13.5%) were considered severe in intensity. Serious Adverse Events: Overall, 40 subjects (25.8%) experienced 58 treatment-emergent serious adverse events. Cataract (3 subjects, 5 events) and cholelithiasis (3 subjects, 3 events) were the most frequent serious adverse events. There were two serious adverse events of hyperglycemia and one each of hypoglycemia, nausea, and vomiting. Only two serious adverse events (nausea and vomiting) were considered to be possibly related to study medication by the investigator. One subject who completed 52 weeks of exenatide treatment died as a result of being struck by an automobile while crossing the street. Two subjects died as a result of malignancies following withdrawal from the study. One subject was withdrawn subsequent to the diagnosis of bladder cancer, and died 44 days after withdrawal; another subject was diagnosed with pancreatic cancer approximately 2 months after withdrawal from the study, and died several weeks later. None of the deaths were assessed by the investigator as being related to study medication. Adverse Events Leading to Withdrawal: Overall, 28 (18.1%) subjects withdrew from the study as a result of a TEAE; a majority of these occurred as a single instance in any given adverse event category. Categories of preferred terms that included more than one withdrawal were hyperglycemia (five subjects), nausea (four subjects), vomiting (three subjects), and diabetes mellitus inadequate control (two subjects). Nine of the events leading to withdrawal were considered serious by the investigator. Anti-Exenatide Antibodies: The emergence of anti-exenatide antibodies did not appear to have an adverse impact on either efficacy or safety.

Conclusions: This open-label study of exenatide given by SC injection BID in subjects with type 2 diabetes treated with metformin, a sulfonylurea, or a metformin/sulfonylurea combination supports the following conclusions:

- Glycemic control was improved and the effect was durable through 132 weeks of treatment.
- Fasting plasma glucose concentrations decreased rapidly upon initiation of therapy. This reduction was generally sustained throughout the study.
- Weight loss was maintained over 132 weeks of exenatide therapy.
- Improvements in fasting lipids were observed after increasing exposure to exenatide; the improvements were most pronounced after 132 weeks of treatment.
- Adverse events were primarily transient and mild in intensity.
- Nausea was typically mild to moderate in intensity and decreased over time.
- All hypoglycemic events were typically mild to moderate in intensity with the exception of one severe event. The prevalence was lowest in subjects using metformin alone as an adjunct oral antidiabetic drug.
- The emergence of anti-exenatide antibodies did not appear to have an adverse impact on either efficacy or safety.

Exenatide 10 µg BID given by SC injection appeared to be generally safe and have sustained efficacy through 132 weeks of treatment in subjects with type 2 diabetes whose glycemic control was suboptimal when treated with metformin alone, a sulfonylurea alone, or a combination of metformin and a sulfonylurea.

This study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice.