Safety and efficacy of twice-daily exenatide in Taiwanese patients with inadequately controlled type 2 diabetes mellitus

Chieh-Hsiang Lu a, Ta-Jen Wu b, Kuang-Chung Shih c, Ewan Ni d, Victoria Reed e, Maria Yu f, Wayne H.-H. Sheu g, Lee-Ming Chuang h,*

a Chia-Yi Christian Hospital, Chia-Yi, Taiwan
b National Cheng-Kung University Hospital, Tainan, Taiwan
c Division of Endocrinology and Metabolism, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan
d Eli Lilly and Company (Taiwan) Inc., Taipei, Taiwan
e Eli Lilly and Company, Sydney, Australia
f Eli Lilly Canada Inc., Toronto, Canada
g Endocrinology and Metabolism, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan
h Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

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KEYWORDS
- glucagon-like peptide 1
- Taiwan
- type 2 diabetes mellitus

Background/Purpose: Exenatide has been predominantly studied in non-Asian populations. The purpose of this study was to investigate the safety and efficacy of twice-daily (BID) exenatide versus placebo in a subpopulation of Taiwanese patients from a larger study on Asian patients.

Methods: Patients unable to achieve glycemic control with metformin alone or metformin in combination with sulfonylurea were randomly assigned to self-administer either 5 μg exenatide or placebo BID for 4 weeks, then 10 μg exenatide or placebo BID for an additional 12 weeks, in addition to their regular oral therapy.

Results: Fifty patients from Taiwan were enrolled in this study (54.0% male; age: 50.9 ± 9.4 years; weight: 71.0 ± 11.6 kg; 8.1 ± 1.0% hemoglobin A1c (HbA1c)). The exenatide-treated patients demonstrated a statistically significant greater reduction in HbA1c from baseline to the endpoint (least-squares [LS] mean [95% confidence interval (CI)]: -0.8% [-1.4--0.2]; p = 0.009) compared with patients who received placebo (LS mean [95% CI]: -0.1% [-0.7--0.4]) with an LS mean [95% CI] between-group difference of -0.7% (-1.3--0.1) (p = 0.025). A statistically significant higher number of exenatide-treated patients achieved HbA1c targets of ≤ 7% (p = 0.020) and ≤ 6.5% (p = 0.021) by the endpoint compared with patients who received placebo. Exenatide-treated patients experienced a statistically significant reduction in
Exenatide treatment in Taiwanese patients

Introduction

According to the World Health Organization (WHO), more than 180 million people worldwide have type 2 diabetes mellitus and this number is likely to more than double by the year 2030.1 Asia is predicted to be the center of this epidemic.2 Rapid socioeconomic progress, as seen in Taiwan over the past 30 years, as well as the adoption of unhealthy lifestyles, migration to industrialized counties, the increasing prevalence of child obesity, and other sociocultural factors are associated with the substantial increase in the prevalence of diabetes in Taiwan.3,4

Exenatide is a glucagon-like peptide 1 (GLP-1) agonist that has been approved for use in a number of countries, including the United States (for use as a monotherapy or in combination with metformin [MET] and/or sulfonylurea [SU] or thiazolidinedione in combination with diet and exercise) and Europe (in combination with MET and/or SU or in combination with thiazolidinedione and/or MET), to improve glycemic control in patients with type 2 diabetes mellitus who have not achieved adequate glycemic control. Exenatide is a 39-amino acid peptide with several potentially beneficial glucoregulatory actions similar to those of the endogenous GLP-1, including reducing circulating glucose, enhancing insulin secretion, suppressing inappropriately elevated glucagon secretion, decelerating gastric emptying, and enhancing satiety.5–10 Decreased food intake and weight loss are additional beneficial effects associated with exenatide treatment.11–13

The majority of patients with type 2 diabetes mellitus are already obese, which contributes to the development of insulin resistance and lipotoxicity. Weight gain is associated with an increased incidence of cardiovascular disease risk factors, such as hypertension and dyslipidemia; however, some therapies currently used to maintain and improve glycemic control, such as thiazolidinediones, sulfonylureas, and insulins, are associated with weight gain.14 Potential weight gain in association with glycemic control therapy can be a major barrier to successful treatment compliance.15

The safety and efficacy of exenatide has been predominantly studied in non-Asian populations.11–13,16–18 However, the results of a clinical study (ClinicalTrials.gov registration no. NCT00324363) that investigated the safety and efficacy of exenatide in Asian countries have recently been published.19 The objective of this double-blind, placebo-controlled, randomized, two-arm, parallel study was to test the hypothesis that exenatide, when taken twice-daily (BID) before morning and evening meals, produces a greater baseline-to-endpoint reduction in glycosylated hemoglobin (HbA1c) than placebo BID after 16 weeks of treatment in Asian patients with type 2 diabetes mellitus that was inadequately controlled using MET alone or MET in combination with SU.

Because Taiwan is culturally and geographically distinct from other Asian countries, a subanalysis was conducted to investigate the efficacy and safety of exenatide in Taiwanese patients, the results of which are presented here.

Materials and methods

Patients were recruited to participate in this double-blind, placebo-controlled, randomized, two-arm, parallel study from four Asian countries (China, India, Korea, and Taiwan) between January 2006 and February 2007. This report presents data related to the 51 randomized patients recruited from Taiwan.

All patients (both women and men) enrolled in this study were between 21–75 years of age (inclusive), met the WHO criteria for type 2 diabetes mellitus, had been treated with a stable dose of MET alone or in combination with SU for at least 3 months prior to screening, and demonstrated suboptimal glycemic control (HbA1c between 7.1–11.0%, inclusive).20

Patients were not eligible for enrollment if they had been treated with exogenous insulin for more than 1 week within the 3 months prior to screening, had a clinically significant history of cardiac or renal disease, demonstrated active cardiac disease within 1 year prior to inclusion in the study, had a history of renal transplantation, were currently receiving renal dialysis, or had an elevated serum creatinine level (> 133 μmol/L for men or > 106 μmol/L for women).

Patients receiving thiazolidinediones, meglitinide derivatives, alpha-glucosidase inhibitors, systemic corticosteroids, or drugs that directly affect gastrointestinal motility were also excluded. Pregnant or breastfeeding women were not eligible, and all women of childbearing potential were required to use an approved method of birth control.

This study (ClinicalTrials.gov registration no. NCT00324363) was approved by the ethical review board of each participating hospital and carried out in accordance with the ethical principles of the Declaration of Helsinki and...
are consistent with clinical practices and Taiwanese laws and regulations. All patients provided signed informed consent before undergoing any study procedures.

After a 1-week screening period, the patients entered a 2-week, single-blind, placebo lead-in period to acclimate those who were injection-naive. On the third visit, patients were stratified by investigative site and current treatment (MET or MET/SU) and randomly assigned with equal probability to one of two treatment groups (current treatment plus exenatide or current treatment plus placebo) by a computer-generated randomization sequence using an interactive voice response system.

In addition to their regular glycemic control treatment regimen (MET or MET/SU), patients were required to self-administer an injection of 5 μg (in 20 μL of solution) BID of exenatide or 20 μL placebo for the first 4 weeks of therapy followed by 10 μg (in 40 μL of solution) BID of exenatide or 40 μL placebo for an additional 12 weeks of therapy.

The primary outcome of this study was the baseline-to-endpoint reduction in HbA1c obtained by exenatide versus placebo BID after 16 weeks of treatment. Secondary outcomes included the proportion of patients who achieved a HbA1c target of ≤ 7% and ≤ 6.5%, changes in body weight, fasting plasma glucose (FPG), a 7-point self-monitored blood glucose (SMBG) profile, and the safety and tolerability of exenatide versus placebo (as measured by the incidence and rate of hypoglycemic events, treatment-emergent adverse events [TEAEs], and clinical laboratory analytes).

Hypoglycemic episodes were defined as any time a patient experienced a sign or symptom of hypoglycemia with or without a documented blood glucose level of < 3.3 mmol/L (60 mg/dL) during self-monitoring or treatment. Severe hypoglycemia was defined as an episode of symptoms that required the assistance of another person and was associated with either a glucose level of < 2.8 mmol/L (50 mg/dL) or prompt recovery after the administration of oral carbohydrates, intravenous glucose, or intramuscular glucagon.

Efficacy and safety analyses were conducted on the full analysis set (FAS), which included all randomized patients who self-administered at least one dose of the study drug. Efficacy analyses were also performed on the per-protocol analysis set (PPS) for supportive evidence. All statistical tests were performed at a level of significance of 0.05. No adjustments were made for multiplicity. Missing data were not included in the analysis, except for the last observation carried forward (LOCF) of the postbaseline values.

Treatment comparisons of the primary and secondary efficacy measures were made using the analysis of covariance model, including treatment, pooled investigator, oral antidiabetic therapy (OAD) stratum, and baseline values of the dependent variables as covariates. Least-squares (LS) means with 95% confidence intervals (CI) were produced to estimate the treatment effects. The superiority of exenatide was demonstrated if an LS mean indicated a greater reduction in HbA1c for exenatide than placebo and a p value of < 0.05 (2-sided) was determined. The percentage of patients who achieved the target HbA1c value (≤ 7%) at the endpoint was summarized and the differences in the proportions between the treatment groups was examined using logistic regression in terms of treatment, OAD stratum, and baseline HbA1c.

Results

Patient disposition and baseline characteristics

In Taiwan, 51 patients were randomly assigned to the two treatment groups. Of these patients, 26 received exenatide BID (exenatide group), 24 received placebo (placebo group), and one patient (assigned to the placebo group) was dropped from the study prior to taking the first dose of the study therapy. Forty-four (88.0%) patients completed the 16-week treatment period (placebo group: 20 [83.3%]; exenatide group: 24 [92.3%]). Details regarding patient disposition are presented in Fig. 1.

The baseline demographic characteristics are similar between the two treatment groups (Table 1). At baseline, 54.0% of patients were men and demonstrated a mean ± standard deviation (SD) of 50.9 ± 9.4 years of age, 27.2 ± 3.3 kg/m² body mass index (BMI), 8.1 ± 1.0% overall HbA1c, and a history of diabetes of 7.6 ± 4.9 years. Seventy-two percent of patients had a BMI ≥ 25.

With respect to OAD medication, the majority of patients were taking MET/SU at baseline (Table 1). The average daily dose of MET at baseline was similar between groups (1706 mg/day for the placebo group vs. 1692 mg/day for the exenatide group).

Efficacy measures

Patients treated with exenatide experienced a statistically significant reduction in HbA1c from baseline to the endpoint (LS mean [95% CI]: -0.8% [-1.4—-0.2]; p = 0.009), while no significant difference was observed in the placebo group (LS mean [95% CI]: -0.1% [-0.7—-0.4]; Table 2). A statistically significant mean LS between-treatment difference (exenatide-placebo) in HbA1c from the baseline of -0.7% (95% CI: -1.3—-0.1; p = 0.025) was observed at the endpoint.

A statistically and significant greater percentage of exenatide-treated patients reported endpoint HbA1c targets of ≤ 7% (exenatide: 56.5%; placebo: 26.1%; p = 0.020) and ≤ 6.5% (exenatide: 42.3%; placebo: 13.0%; p = 0.021) compared with placebo-treated patients.

After 16 weeks of treatment, exenatide-treated patients demonstrated statistically significant reductions in body weight from the baseline (LS mean [±SEM] change of -1.99 ± 0.53 kg) compared with placebo-treated patients (LS mean [±SEM] change of -0.37 ± 0.50 kg; p < 0.001). A statistically significant mean LS between-treatment difference (exenatide-placebo) in terms of body weight reduction from baseline of -1.6 kg (95% CI: -2.7—-0.6; p = 0.004) was observed at the endpoint.

Baseline-to-endpoint reductions in fasting plasma glucose were not significantly different between the two treatment groups (Table 2). The 7-point self-monitored blood glucose profiles of the Taiwanese patients (Fig. 2) were less variable at the endpoint than at baseline among patients treated with exenatide, but not among patients treated with placebo. At the end of the study, the LS mean differences (95% CI; exenatide-placebo) in terms of the SMBG values were -3.63 (-5.18—-2.07; p < 0.001), -0.27 (-1.72—1.18; p = 0.710), and -2.29 (-3.99—-0.59; p = 0.009)
for the postbreakfast, postlunch, and postdinner reference points, respectively. The LS mean difference (95% CI; exenatide-placebo) for the daily mean at the end of the study was -1.03 (-2.04, -0.02; p = 0.046). These results are similar to those of the patients in the overall population.

**Safety**

In this Taiwanese patient population, 13 (50.0%) exenatide-treated patients and nine (37.5%) placebo-treated patients reported one or more TEAEs. The most frequently reported (total incidence ≥ 5) TEAEs included nausea (exenatide, 4 [15.4%]; placebo, 0 [0.0%]), cough (exenatide, 2 [7.7%]; placebo, 1 [4.2%]), diarrhea (exenatide, 2 [7.7%]; placebo, 1 [4.2%]), constipation (exenatide, 2 [7.7%]; placebo, 0 [0.0%]), decreased appetite, (exenatide, 2 [7.7%]; placebo, 0 [0.0%]), and dizziness (exenatide, 2 [7.7%]; placebo, 0 [0.0%]).

Of the four exenatide-treated patients who experienced nausea, one case was of mild severity and three cases were of moderate severity (3.8% and 11.5%, respectively). The highest incidence of nausea was reported when patients initiated 5 mg exenatide at week 0 and increased the dose to 10 mg at week 4. One patient (3.8%) was dropped from the study due to diarrhea, which started the day after initiating exenatide therapy and was moderate in intensity. No deaths occurred during this study.

The incidence of symptomatic hypoglycemic episodes was numerically higher among exenatide-treated patients (12 [46.2%]) compared with placebo-treated patients (1 [4.2%]). The symptomatic hypoglycemia rate per patient (mean ± SD), when adjusted for 30 days, was higher in the exenatide group (0.40 ± 0.61) than the placebo group (0.02 ± 0.11) after 16 weeks of treatment; when adjusted for 1 year, the symptomatic hypoglycemia rate per patient (mean ± SD) was 4.86 ± 7.36 among exenatide-treated patients compared with 0.27 ± 1.32 for placebo-treated patients.

All hypoglycemic episodes were reported by patients taking a combination of MET plus SU; however, only five patients in Taiwan were administered MET alone. No patients in Taiwan experienced a severe hypoglycemic episode during this study.

The relationship between the development of anti-exenatide antibodies and glycemic control was also examined. Among patients who tested positive (n = 9) or negative (n = 17) for anti-exenatide antibodies, the change...
The results of this subanalysis of Taiwanese patients demonstrates that exenatide BID is superior to placebo for the management of glycemic control in patients with type 2 diabetes mellitus who failed to achieve control on OADs after 16 weeks of treatment. These findings are consistent with results of the overall study on patients in both East and West Asia and similar trials that have been performed on non-Asian populations: specifically, a significant reduction in HbA1c was observed and significantly more exenatide-treated patients were able to meet the HbA1c targets of ≤7% and ≤6.5% when compared with placebo-treated patients at the endpoint. No patients in the Taiwanese subset discontinued participation in the study due to the lack of efficacy; however, one patient discontinued treatment due to adverse effects. Exenatide-treated Taiwanese patients experienced a significantly greater reduction in mean body weight compared with placebo. It is interesting to note that of the four countries (China, India, Korea, and Taiwan) that participated in the overall study, patients in Taiwan experienced the largest reduction in body weight by the study end; however, due to the small sample size, additional studies are required to further investigate this finding. The significant reduction in body weight observed among exenatide-treated patients in Taiwan are in accordance with previous studies on both non-Asian and Asian populations, suggesting that reductions in body weight cannot be attributable to ethnic differences but may be a consistent result of exenatide treatment. These data support previously published results indicating the additional benefit of exenatide over other glycemic control therapies, such as insulin, which are often correlated with weight gain. Additional weight gain in patients with type 2 diabetes mellitus who are already overweight or obese can also have a negative impact on treatment compliance and quality of life.

In Taiwan, as in the overall study, more exenatide- than placebo-treated patients reported TEAEs. The most frequently reported TEAE was nausea of mild to moderate severity, which decreased over time, a finding that is

### Table 2  Summary of baseline-to-endpoint mean changes of the efficacy measures.

<table>
<thead>
<tr>
<th></th>
<th>Exenatide (N = 26)</th>
<th>Placebo (N = 24)</th>
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</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, mean ± SD</td>
<td>8.1 ± 1.0</td>
<td>8.1 ± 1.0</td>
</tr>
<tr>
<td>Endpoint △, LS mean (95% CI)</td>
<td>-0.8 (-1.4—0.2)</td>
<td>-0.1 (-0.7—0.4)</td>
</tr>
<tr>
<td>Fasting plasma glucose, mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, mean ± SD</td>
<td>9.1 ± 2.4</td>
<td>9.1 ± 2.8</td>
</tr>
<tr>
<td>Endpoint △, LS mean (95% CI)</td>
<td>-0.6 (-2.3—1.0)</td>
<td>-0.3 (-1.9—1.3)</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, mean ± SD</td>
<td>71.6 ± 8.9</td>
<td>70.4 ± 14.1</td>
</tr>
<tr>
<td>Endpoint △, LS mean (95% CI)</td>
<td>-2.0 (-3.1—0.9)</td>
<td>-0.4 (-1.4—0.6)</td>
</tr>
<tr>
<td>Mean daily glucose,a mmol/L</td>
<td>10.8 ± 2.9</td>
<td>10.8 ± 2.4</td>
</tr>
<tr>
<td>Baseline, mean ± SD</td>
<td>8.2 ± 0.5</td>
<td>9.2 ± 0.5</td>
</tr>
</tbody>
</table>

Abbreviations: △, change from baseline; CI, confidence interval; HbA1c, glycosylated hemoglobin; LS, least-squares; N, total number of patients; SD, standard deviation; SE, standard error.

a The values for mean daily glucose are not the mean change.
consistent with previously published data as well as the data obtained in the overall study.11–13,19,22

Taiwanese patients reported a lower overall rate of TEAEs, including a lower rate of nausea in comparison with the overall population, but Taiwanese patients also reported the highest incidence of nausea when initiating 5 µg exenatide (week 0) and at week 4. Whereas, in the overall study, the highest incidence of nausea was reported when patients increased the exenatide dose from 5 µg to 10 µg (week 4) and at week 8. It is possible that these disparities may be due to ethnic differences between countries; however, due to the small sample size, further studies are necessary to confirm this hypothesis. Initiating exenatide therapy at a lower dose could be a potential option that clinical practices should consider in Taiwan, but further studies are required to verify this hypothesis.

In Taiwan, the largest meal of the day is traditionally dinner; however, Taiwanese patients demonstrated a similar SMBG profile to that of patients in the overall Asian population. This suggests that meal patterns may not be so different between the four countries that were investigated, or it may be that the efficacy of exenatide is unaffected by variations in meal size.19,23

In both the overall study population and the Taiwanese subset, the incidence of symptomatic hypoglycemic episodes was higher among exenatide-treated patients compared with the placebo group. The incidence of hypoglycemic episodes was higher among patients taking a combination of MET/SU in the Taiwanese subset and in the overall study population. In the Taiwanese population, however, only a small number of patients were taking MET alone. No Taiwanese patient experienced severe hypoglycemia. The main limitation of this analysis is the small number of Taiwanese patients who participated in this study. The findings and conclusions drawn from these country-specific results should, therefore, be evaluated and interpreted with consideration to the overall study results.

In conclusion, the findings of this subgroup analysis of Taiwanese patients are consistent with the overall study results, which show that exenatide (10 µg/day BID) is superior to placebo for improving glycemic control in patients with type 2 diabetes mellitus who experienced inadequate glycemic control with OAD therapy (MET alone or MET in combination with SU).

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