Original Article: Treatment

Dose-dependent effects of the once-daily GLP-1 receptor agonist lixisenatide in patients with Type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled trial

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Accepted 17 April 2010

Abstract

Aims To evaluate the dose–response relationship of lixisenatide (AVE0010), a glucagon-like peptide-1 (GLP-1) receptor agonist, in metformin-treated patients with Type 2 diabetes.

Methods Randomized, double-blind, placebo-controlled, parallel-group, 13 week study of 542 patients with Type 2 diabetes inadequately controlled [glycated haemoglobin (HbA1c) ≥ 7.0 and < 9.0% (≥ 53 and < 75 mmol/mol)] on metformin (≥ 1000 mg/day) treated with subcutaneous lixisenatide doses of 5, 10, 20 or 30 μg once daily or twice daily or placebo. The primary end-point was change in HbA1c from baseline to 13 weeks in the intent-to-treat population.

Results Lixisenatide significantly improved mean HbA1c from a baseline of 7.55% (59.0 mmol/mol); respective mean reductions for 5, 10, 20 and 30 μg doses were 0.47, 0.50, 0.69 and 0.76% (5.1, 5.5, 7.5 and 8.3 mmol/mol), on once-daily and 0.65, 0.78, 0.75 and 0.87% (7.1, 8.5, 8.2 and 9.5 mmol/mol) on twice-daily administrations vs. 0.18% (2.0 mmol/mol) with placebo (all P < 0.01 vs. placebo). Target HbA1c < 7.0% (53 mmol/mol) at study end was achieved in 68% of patients receiving 20 and 30 μg once-daily lixisenatide vs. 32% receiving placebo (P < 0.0001). Dose-dependent improvements were observed for fasting, postprandial and average self-monitored seven-point blood glucose levels. Weight changes ranged from −2.0 to −3.9 kg with lixisenatide vs. −1.9 kg with placebo. The most frequent adverse event was mild-to-moderate nausea.

Conclusions Lixisenatide significantly improved glycaemic control in mildly hyperglycaemic patients with Type 2 diabetes on metformin. Dose–response relationships were seen for once- and twice-daily regimens, with similar efficacy levels, with a 20 μg once-daily dose of lixisenatide demonstrating the best efficacy-to-tolerability ratio. This new, once-daily GLP-1 receptor agonist shows promise in the management of Type 2 diabetes to be defined further by ongoing long-term studies.

Diabet. Med. 27, 1024–1032 (2010)

Keywords glucagon-like peptide-1 receptor agonist, glycaemic control, lixisenatide, Type 2 diabetes

Abbreviations DPP-4, dipeptidyl-peptidase-4; GLP-1, glucagon-like peptide-1; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; NGSP, National Glycohemoglobin Standardization Program; QD, once daily

Introduction

Glycaemic control in Type 2 diabetes mellitus is generally targeted toward a glycated haemoglobin (HbA1c) level as close to normal [i.e. < 6.5 or < 7.0% (< 48 or < 53 mmol/mol)] as safely as possible [1,2]. Although a variety of pharmacological approaches are now available, current management often fails to
achieve glycaemic targets [3]. Analogues of the hormone glucagon-like peptide-1 (GLP-1) have shown promise as therapeutic options in Type 2 diabetes. Endogenous GLP-1 enhances insulin secretion and inhibits postprandial glucagon secretion in a glucose-dependent fashion, slows gastric emptying, reduces food intake and promotes weight loss, with all these effects matched by GLP-1 receptor agonists [4,5]. The suppression of glucagon by GLP-1 does not occur at hypoglycaemic glucose levels, and as such exogenous GLP-1 does not impair the physiological mechanisms that counteract hypoglycaemia [6].

Pharmacological replacement with GLP-1 receptor agonists in patients with Type 2 diabetes represents an attractive strategy to improve metabolic control, particularly as we aim for near-normal glycaemia, with less risk of hypoglycaemia and no weight gain or, ideally, weight loss. In addition to improving glycaemic control, GLP-1 receptor agonists have the potential to preserve pancreatic islet B cells by enhancing proliferation and inhibiting apoptosis, based on preclinical studies in animal models and cultured pancreatic B cells [7–12], but still with no evidence in human studies.

However, exogenous native GLP-1 is not suitable as a therapeutic agent because it is rapidly degraded by dipeptidyl peptidase-4 (DPP-4) and has a half-life of less than 2 min [4]. Thus, DPP-4-resistant GLP-1 receptor agonists with extended half-lives have been developed. Lixisenatide (AVE0010) is a new, potent, selective and synthetic 44 amino acid exendin-4-like GLP-1 receptor agonist modified C-terminally with six Lys residues and one Pro deleted. In Chinese hamster ovary (CHO) cells transfected with the human GLP-1 receptor, lixisenatide had a binding affinity approximately 4-fold greater than that of native human GLP-1 (IC50 for lixisenatide = 1.43 nmol/l vs. IC50 for GLP-1 = 5.48 nmol/l) [9,13]. Lixisenatide is being developed with the aim of improving the management of Type 2 diabetes. The primary objective of this study was to evaluate thoroughly the dose–response effect of lixisenatide using once- or twice-daily regimens (5–30 μg once or twice daily) on HbA1c changes over 13 weeks in metformin-treated patients with Type 2 diabetes.

**Patients and methods**

**Study participants**

The study population comprised male and female patients aged 30–75 years with Type 2 diabetes mellitus of at least 1 year’s duration inadequately controlled [HbA1c ≥ 7.0 and < 9.0% (≥ 53 and < 75 mmol/mol) on stable metformin monotherapy (≥ 1000 mg/day) for at least 3 months prior to screening. The main exclusion criteria were as follows: history of gastrointestinal disease with prolonged nausea and vomiting during the previous 6 months; history of chronic pancreatitis or stomach/gastric surgery; severe cardiovascular events during the previous 6 months; or hepatic or renal disease at screening [serum creatinine ≥ 114.4 μmol/l (1.5 mg/dl) for males and ≥ 106.8 μmol/l (1.4 mg/dl) for females].

The study was approved by the institutional review boards or ethics committees and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients gave written informed consent to participate in the study.

**Study design**

This 13 week, multinational, randomized, parallel-group, placebo-controlled study was conducted at 133 centres between March 2006 and August 2007. The study drug, added-on to stable metformin, was double-blind regarding active treatment or placebo and open-label regarding the treatment volume.

Following a 2 week screening phase, eligible patients entered into a 2 week, single-blind, placebo run-in period. Eligible patients were then randomized at visit 4 (week 0) to one of 12 treatment arms (2:2:2:2:2:2:1:1:1:1:1:1): to subcutaneous injections of lixisenatide doses of 5, 10, 20 or 30 μg administered once daily within 1 h before breakfast (with volume-matched placebo before dinner); to lixisenatide doses of 5, 10, 20 or 30 μg administered twice daily (10, 20, 40 or 60 μg total daily dose, respectively) within 1 h before both breakfast and dinner; or to one of four volume-matched placebo treatments administered twice daily.

Randomization of subjects, allocation of medication and management of drug supplies were performed using an interactive voice response system.

Dose escalation was performed during the first 2–4 weeks for patients randomized to 20 and 30 μg dose levels of the study medication; the dose was initiated at 10 μg for 1 week and increased by 5 μg/week up to the target dose. The entry dosage of metformin remained unchanged throughout the study. All patients received diet and lifestyle counselling according to the American Diabetes Association guidelines [1].

**Study assessments**

The primary efficacy end-point was change in HbA1c from baseline to study end for the intent-to-treat population. Glycated haemoglobin was measured at a National Glycohemoglobin Standardization Program (NGSP) Level 1 certified central laboratory, measured with the high-performance liquid chromatography method. Corresponding International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) standardized values were calculated using the relationship: IFCC value (in mmol/mol) = (NGSP value – 2.152)/0.09148 [14,15]. All HbA1c data are given as NGSP standardized values and IFCC values. The secondary efficacy measures included the percentage of patients achieving an HbA1c < 7.0 or < 6.5% (< 53 or < 48 mmol/mol), changes in body weight, fasting plasma glucose, and 2 h post-prandial plasma glucose after a standardized breakfast. Self-monitored seven-point blood glucose measurements were performed at baseline and week 13. Anti-lixisenatide antibody levels were measured.

Safety and tolerability were assessed by physical examination, adverse event reporting, blood pressure, heart rate, 12-lead
electrocardiogram and standard laboratory measurements. Symptomatic hypoglycaemia was defined as symptoms consistent with hypoglycaemia, with an accompanying blood glucose < 3.3 mmol/l or prompt recovery with carbohydrate.

Statistical analyses

Sample sizes of 50 patients in each active treatment group and 100 patients in the placebo group were calculated to provide a statistical power of 81% to detect a 0.6% (6.6 mmol/mol) difference in HbA1c between an active treatment and placebo assuming a standard deviation of 1.2% (13.1 mmol/mol). Statistical significance was assumed at the 5% level.

Analyses of the primary efficacy variable (changes in HbA1c from baseline to end-point) were performed using analysis of covariance (ANCOVA) model, with treatment and country as fixed factors and baseline HbA1c as a covariate. Multiple testing procedure was used for the primary efficacy variable in order to control Type 1 error for the study and for multiple doses within procedure was used for the primary efficacy variable in order to control Type 1 error for the study and for multiple doses within procedure. The continuous test was used from the above ANCOVA model to assess dose–response Type 1 error for the study and for multiple doses within procedure was used for the primary efficacy variable. Data from placebo-treated subjects were pooled for statistical analysis. Both methods used for the primary efficacy variable. Data from one on-treatment value for efficacy variables); they are presented as least one dose of the study medication and having a baseline and the intent-to-treat population (all randomized subjects taking at least one dose of the study medication and from baseline to end-point) were performed using analysis of covariance (ANCOVA) model, with treatment and country as fixed factors and baseline HbA1c as a covariate. Multiple testing procedure was used for the primary efficacy variable in order to control Type 1 error for the study and for multiple doses within each dose regimen (once and twice daily). The step-down trend test was used from the above ANCOVA model to assess dose–response relationship within each regimen. The continuous secondary efficacy variables (change in body weight, fasting plasma glucose, seven-point self monitored blood glucose and post-prandial plasma glucose) were analysed using the same methods used for the primary efficacy variable. Data from placebo-treated subjects were pooled for statistical analysis. Both means and least square adjusted means were calculated. The percentages of patients achieving an HbA1c < 7.0 and < 6.5% (< 53 and < 48 mmol/mol) were analysed using a Cochran–Mantel–Haenszel test stratified by country. Safety and tolerability data were analysed using descriptive statistics for all patients who received at least one dose of study medication.

Unless otherwise indicated, all efficacy data were analysed in the intent-to-treat population (all randomized subjects taking at least one dose of the study medication and having a baseline and one on-treatment value for efficacy variables); they are presented as means ± SEM, unless specified otherwise.

Results

Demographic and baseline characteristics

A total of 542 patients were randomized from 1466 patients screened. The reasons for screening failure (n = 924) were as follows: ineligible inclusion criteria (n = 850), patient’s wish (n = 34) and other (n = 40). Approximately 90% of patients completed 13 weeks of active treatment, and the percentages ranged from 83% in the 30 μg lixisenatide once daily group to 96% in the 5 μg lixisenatide once daily and twice daily groups, compared with 95% in the placebo group (Table 1). Nearly all patients were at their randomized dose level by study end, ranging from 85 and 89% in the 30 μg once daily and twice daily groups to 100% in the 5 μg once daily and twice daily and 10 μg twice daily groups.

Demographic and baseline characteristics were well matched, and there were no clinically relevant differences between groups (Table 1).

Efficacy

There were significantly greater improvements in the primary efficacy end-point of HbA1c change from a mean overall baseline of 7.55% (59.0 mmol/mol) in all the lixisenatide groups (P < 0.01 vs. placebo), with reductions ranging from 0.47 to 0.87% (from 5.1 to 9.5 mmol/mol) among the different dosing regimens (mean reductions for 5, 10, 20 and 30 μg doses of 0.47, 0.50, 0.69 and 0.76% [5.1, 5.5, 7.5 and 8.3 mmol/mol] on once-daily administration, respectively, and 0.65, 0.78, 0.75 and 0.87% (7.1, 8.5, 8.2 and 9.5 mmol/mol) on twice-daily administration, respectively), compared with a decrease of 0.18% (2.0 mmol/mol) for placebo (Fig. 1). A dose-response relationship with HbA1c level was seen for both the once daily and twice daily regimens of lixisenatide, with improvements in HbA1c observed as early as week 5 (Fig. 1).

Significantly more patients in the lixisenatide groups achieved an HbA1c < 7.0% (53 mmol/mol) ranging from 47 to 69% with once daily dosing and from 51 to 77% with twice daily dosing), compared with 32% of those in the placebo group (P < 0.05) at week 13 (Fig. 2). Further improvement in glycaemic control to HbA1c < 6.5% (48 mmol/mol) at study end was observed in significantly more patients in the lixisenatide groups than in the placebo group (7.5%); one-third of patients receiving 20 or 30 μg once daily and 5, 10 and 20 μg twice daily achieved this goal (P < 0.0001 for all of these groups vs. placebo and P = 0.0315 vs. placebo for 5 μg once daily; Fig. 2).

As noted in Table 2, there were dose-dependent reductions from baseline in fasting plasma glucose and also in daily averaged seven-point self monitored blood glucose, 2 h post-prandial plasma glucose concentrations, and in body weight with lixisenatide.

Safety and tolerability

The most frequent adverse events were gastrointestinal, primarily dose-dependent nausea (Table 3). The onset of gastrointestinal adverse reactions was observed during the first 5 weeks of the study in the majority of cases, and these were usually mild-to-moderate in intensity. No cases of pancreatitis were experienced. There was no evidence of a dose relationship with symptomatic hypoglycaemic episodes [ranging from 1 to 3 events (0.9–5.7%) per group], which were mostly mild in intensity. No patients experienced severe hypoglycaemia.

There were zero to three (5.6%) serious adverse events in the lixisenatide groups and three (2.8%) in the placebo group (Table 3). These events included one patient in the lixisenatide 30 μg once daily group who discontinued treatment owing to a few seconds of loss of consciousness and one in the lixisenatide 10 μg once daily group who discontinued secondary to an allergic reaction (a 30 min episode of pruritus over the entire
### Table 1  Patient disposition, demographics and baseline characteristics (safety population)

| Lixisenatide | Placebo | 5 µg QD | 10 µg QD | 20 µg QD | 30 µg QD | 5 µg BID | 10 µg BID | 20 µg BID | 30 µg BID |
|--------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| Patient disposition, n (%) | 109 | 55 | 52 | 55 | 54 | 53 | 56 | 54 | 54 |
| Complete | 103 (94.5) | 53 (96.4) | 47 (90.4) | 46 (83.6) | 45 (83.3) | 51 (96.2) | 51 (91.1) | 46 (85.2) | 47 (87.0) |
| Discontinued | 6 (5.5) | 2 (3.6) | 5 (9.6) | 9 (16.4) | 9 (16.7) | 2 (3.8) | 5 (8.9) | 8 (14.8) | 7 (13.0) |
| Reasons for discontinuation, n (%) | | | | | | | | | |
| Adverse event | 2 (1.8) | 1 (1.8) | 2 (3.8) | 3 (5.5) | 6 (11.1) | 0 | 2 (3.6) | 8 (14.8) | 5 (9.3) |
| Lack of efficacy | 0 | 1 (1.8) | 0 | 0 | 1 (1.9) | 0 | 0 | 0 | 0 |
| Other | 4 (3.7) | 0 | 3 (5.8) | 6 (10.9) | 2 (3.7) | 2 (3.8) | 3 (5.4) | 0 | 2 (3.7) |

**Demographics and baseline characteristics**

| Mean age (years ± SD) | 56.3 ± 9.2 | 56.8 ± 7.8 | 55.4 ± 9.2 | 55.4 ± 9.9 | 56.5 ± 8.7 | 57.1 ± 8.2 | 56.0 ± 7.9 | 56.7 ± 8.3 | 55.3 ± 9.1 |
| Male, n (%) | 61 (56.0) | 26 (47.3) | 31 (59.6) | 28 (50.9) | 27 (50.0) | 25 (47.2) | 29 (51.8) | 20 (37.0) | 23 (42.6) |
| Race, n (%) | | | | | | | | | |
| Caucasian | 84 (77.1) | 38 (69.1) | 36 (69.2) | 45 (81.8) | 43 (79.6) | 46 (86.8) | 45 (80.4) | 42 (77.8) | 35 (64.8) |
| Black | 12 (11.0) | 5 (9.1) | 6 (11.5) | 1 (1.8) | 6 (11.1) | 2 (3.8) | 2 (3.6) | 2 (3.7) | 9 (16.7) |
| Other | 13 (11.9) | 12 (21.8) | 10 (19.3) | 9 (16.4) | 5 (9.3) | 5 (9.4) | 9 (16.0) | 10 (18.5) | 10 (18.5) |
| Mean duration of diabetes diagnosis (years ± SD) | 7.1 ± 5.4 | 7.2 ± 4.9 | 6.2 ± 4.1 | 6.4 ± 6.8 | 6.0 ± 4.8 | 6.2 ± 6.0 | 6.4 ± 5.0 | 6.6 ± 5.1 | 7.0 ± 5.4 |
| Mean HbA1c (% ± sd; NGSP) | 7.53 ± 0.6 | 7.58 ± 0.7 | 7.52 ± 0.6 | 7.58 ± 0.7 | 7.60 ± 0.6 | 7.54 ± 0.6 | 7.61 ± 0.7 | 7.46 ± 0.5 |
| Mean HbA1c (mmol/mol ± SD; IFCC)* | 58.8 ± 5 | 59.3 ± 6 | 58.7 ± 5 | 59.3 ± 6 | 58.7 ± 6 | 59.6 ± 5 | 58.9 ± 5 | 59.7 ± 6 | 58.0 ± 4 |
| Mean weight (kg ± sd) | 87.7 ± 14 | 84.6 ± 16 | 90.5 ± 17 | 89.4 ± 17 | 87.6 ± 15 | 86.5 ± 14 | 89.8 ± 17 | 88.5 ± 17 | 87.5 ± 14 |
| Mean BMI (kg/m^2 ± SD) | 31.7 ± 4.2 | 30.7 ± 4.6 | 31.9 ± 4.0 | 32.0 ± 4.3 | 31.6 ± 3.6 | 31.6 ± 4.2 | 32.8 ± 4.4 | 32.7 ± 4.4 | 32.3 ± 4.5 |
| Mean fasting plasma glucose (mmol/l ± SD) | 8.8 ± 2.1 | 8.4 ± 2.1 | 8.7 ± 2.0 | 8.4 ± 1.8 | 8.9 ± 2.1 | 8.9 ± 1.8 | 9.2 ± 2.4 | 9.0 ± 2.0 | 8.8 ± 2.3 |
| Mean 2 h post prandial plasma glucose (mmol/l ± SD) | 11.8 ± 3.2 | 12.8 ± 2.4 | 12.8 ± 3.3 | 11.5 ± 2.5 | 13.1 ± 3.3 | 12.5 ± 2.6 | 12.0 ± 3.3 | 12.3 ± 2.7 | 12.2 ± 3.0 |

**Abbreviations:** IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; NGSP, National Glycohemoglobin Standardization Program; Postprandial plasma glucose measured in a subgroup of patients undergoing standardized breakfast in selected sites. The standardized 300 kcal breakfast, which consisted of orange juice (180 ml), toasted bread (60 g), jam or preserves (20 g), butter or margarine (10 g), whole milk (120 ml) and coffee or tea with non-nutritive sweetener (if desired), was consumed within a 15 min period. The safety population consisted of all randomized patients who took at least one dose of the study medication during the double-blind treatment phase.

* Calculated IFCC standardized HbA1c value (in mmol/mol) = (NGSP value x 2.152)/0.09148 [14,15].
FIGURE 1 Changes in glycated haemoglobin (HbA1c) levels following 13 weeks’ treatment with lixisenatide once daily or twice daily, according to dosage and regimen. Top panel shows change in mean (±SEM) HbA1c over time. Bottom panel shows least square (LS) mean change in HbA1c from baseline to 13 weeks.

FIGURE 2 Percentage of patients with glycated haemoglobin (HbA1c) level of < 7.0% (53 mmol/mol; top panel) and < 6.5% (48 mmol/mol; bottom panel) following 13 weeks’ treatment with lixisenatide once daily or twice daily, according to dosage and regimen.
In this study, the new GLP-1 receptor agonist lixisenatide significantly improved glycemia control. A 4-week, phase 3, randomized, double-blind, placebo-controlled study was performed in patients with Type 2 diabetes inadequately controlled with metformin. A total of 583 patients were randomized in a 1:1:1:1:1 ratio to placebo or to one of the four lixisenatide doses (5, 10, 20, or 30 µg twice daily). At the end of 13 weeks, the least square mean 

| Table 2 | The least square adjusted mean ± SEM changes in fasting plasma glucose, daily averaged self-monitored seven-point blood glucose and 2 h postprandial plasma glucose following 13 weeks of treatment with lixisenatide once daily or twice daily according to dosage and regimen in the ITT population |
|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
|                       | Placebo               | 5 µg QD (n = 55)      | 10 µg QD (n = 51)     | 20 µg QD (n = 53)     | 30 µg QD (n = 52)     | 5 µg BID (n = 51)    | 10 µg BID (n = 54)    | 20 µg BID (n = 52)     | 30 µg BID (n = 53)     |
| Fasting plasma glucose (mmol/l) | -0.21 ± 0.19         | -0.62 ± 0.24         | -0.54 ± 0.25         | -0.80 ± 0.25         | -1.02 ± 0.25         | -0.19 ± 0.24         | -0.98 ± 0.24         | -1.13 ± 0.25         | -1.42 ± 0.25         |
| Average self-monitored seven-point blood glucose (mmol/l) | -0.53 ± 0.18         | -1.23 ± 0.24†        | -1.27 ± 0.24†        | -1.74 ± 0.24†        | -1.77 ± 0.25†        | -0.88 ± 0.24         | -1.60 ± 0.24         | -1.83 ± 0.24         | -2.08 ± 0.24         |
| 2 h postprandial glucose (mmol/l) | -0.41 ± 0.46         | -2.12 ± 0.67†        | -3.57 ± 0.62†        | -3.65 ± 0.68†        | -4.33 ± 0.71†        | -2.01 ± 0.61†        | -3.51 ± 0.62†        | -4.12 ± 0.68†        | -4.61 ± 0.68†        |
| Body weight (kg) | -1.94 ± 0.32         | -2.00 ± 0.40         | -2.39 ± 0.42         | -3.01 ± 0.41†        | -3.47 ± 0.41†        | -2.10 ± 0.41         | -2.21 ± 0.41         | -2.61 ± 0.41         | -3.89 ± 0.41         |

The ITT population consisted of all randomized patients who took at least one dose of the study medication and had a baseline and at least one post-baseline on-treatment value for efficacy variables.

*P < 0.05, †P < 0.01 in the step-down linear trend test.

In a subgroup of patients undergoing standardized breakfast in selected sites (approximately half of total sites). The standardized 500 kcal breakfast, which consisted of orange juice (180 ml), toasted bread (60 g), jam or preserves (20 g), butter or margarine (10 g), whole milk (120 ml) and coffee or tea with non-nutritive sweetener (if desired), was consumed within a 15 min period. Data are mean ± SEM.
In conclusion, in this thorough dose-ranging study of four doses and two regimens, lixisenatide significantly improved glycaemic control in mildly hyperglycaemic patients previously on metformin monotherapy, with associated weight loss and without causing significant hypoglycaemia. Clear dose–response relationships and similar levels of efficacy were seen for the once daily and twice daily regimens, with a 20 µg once daily dose showing the best efficacy-to-tolerability ratio. This new, once-daily GLP-1 receptor agonist shows promising efficacy, safety and tolerability in the management of Type 2 diabetes, but further investigations in long-term studies are needed.

Table 3 Number (%) of patients with treatment-emergent adverse events occurring in ≥10% in any one group and symptomatic hypoglycaemia in the safety population

| Type of adverse event | Placebo (n = 109) | Lixisenatide 5 µg QD (n = 53) | Lixisenatide 10 µg QD (n = 52) | Lixisenatide 20 µg QD (n = 55) | Lixisenatide 30 µg QD (n = 54) | Lixisenatide 5 µg BID (n = 53) | Lixisenatide 10 µg BID (n = 54) | Lixisenatide 20 µg BID (n = 56) | Lixisenatide 30 µg BID (n = 54) |
|-----------------------|-------------------|------------------------------|------------------------------|------------------------------|------------------------------|------------------------------|------------------------------|------------------------------|------------------------------|
| Any treatment-emergent adverse events | 65 (59.6) | 31 (56.4) | 26 (50.0) | 37 (67.3) | 42 (77.8) | 30 (56.6) | 32 (57.1) | 38 (70.4) | 40 (74.1) |
| Any serious treatment-emergent adverse events | 3 (2.8) | 0 | 1 (1.9) | 1 (1.8) | 3 (5.6) | 0 | 1 (1.8) | 2 (3.7) | 0 |
| Nausea | 5 (4.6) | 4 (7.3) | 6 (11.5) | 14 (25.5) | 19 (35.2) | 4 (7.5) | 8 (14.3) | 12 (22.2) | 18 (33.3) |
| Vomiting | 1 (0.9) | 2 (3.6) | 3 (5.8) | 3 (5.5) | 10 (18.5) | 3 (5.7) | 4 (7.1) | 5 (9.3) | 2 (3.7) |
| Diarrhoea | 8 (7.3) | 3 (5.5) | 4 (7.7) | 5 (9.1) | 4 (7.4) | 3 (5.7) | 4 (7.1) | 6 (11.1) | 14 (25.9) |
| Headache | 11 (10.1) | 7 (12.7) | 3 (5.8) | 7 (12.7) | 7 (13.0) | 7 (13.2) | 5 (8.9) | 6 (11.1) | 4 (7.4) |
| Dizziness | 7 (6.4) | 1 (1.8) | 4 (7.7) | 4 (7.3) | 6 (11.1) | 3 (5.7) | 5 (8.9) | 2 (3.7) | 5 (9.3) |
| Symptomatic hypoglycaemia | 1 (0.9) | 1 (1.8) | 2 (3.8) | 1 (1.8) | 1 (1.9) | 3 (5.7) | 1 (1.8) | 3 (5.6) | 1 (1.9) |

Data are n (%). Treatment-emergent adverse events were defined as adverse events that developed or worsened during the on-treatment period (the time from the first dose of study medication up to 3 days after the last dose). The safety population was composed of all randomized patients who took at least one dose of the study medication during the double-blind treatment phase.
**Competing interests**

Dr Ratner has received research support from Amylin, Boehringer Ingelheim, GlaxoSmithKline, Merck, Novo Nordisk, Pfizer, Roche, sanofi-aventis and Takeda Pharmaceuticals, and has acted as a consultant for Amylin, Eli Lilly, Novo Nordisk, Roche, sanofi-aventis and Takeda. Dr Rosenstock has served on advisory boards and received honorarium or consulting fees from Pfizer, Roche, sanofi-aventis, Novo Nordisk, Eli Lilly, MannKind, GlaxoSmithKline, Forest, Takeda, Daichi Sankyo, Boehringer Ingelheim, Johnson & Johnson, Emisphere, Novartis and Amylin. He has also received research grants from Merck, Pfizer, sanofi-aventis, Novo Nordisk, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Forest, Takeda, Novartis, AstraZeneca, Amylin, Johnson & Johnson, Daichi Sankyo, Boehringer Ingelheim and MannKind. Dr Boka is an employee of sanofi-aventis.

The study was funded by sanofi-aventis, the manufacturer of lixisenatide. The investigators and representatives from sanofi-aventis were responsible for the study design, protocol, statistical analysis plans, analysis and reporting of the results. Final responsibility for the decision to submit the manuscript for publication was made jointly by all authors.

**Acknowledgements**

We would like to thank all of the investigators (see below), co-ordinators and patients who took part in this study, Quest Diagnostics (Middlesex, UK) and Van Nuys (CA, USA) for analysing the blood samples for efficacy and safety parameters, and MDS Pharma Services (Fehraltorf, Switzerland) for analysing plasma samples for anti-lixisenatide antibody determination. sanofi-aventis sponsored this study. Editorial support was provided by Susan Crawford.

These data were presented as a poster at the 68th Scientific Sessions of the American Diabetes Association, San Francisco, CA, 6–10 June 2008 and the 44th European Association for the Study of Diabetes, Rome, 7–11 September 2008.

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