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Research: Treatment

Efficacy and safety of lixisenatide once daily vs. placebo in people with Type 2 diabetes insufficiently controlled on metformin (GetGoal-F1)

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Abstract

Aims To assess the efficacy and safety of one- and two-step dose-increase regimens of lixisenatide once daily in participants with Type 2 diabetes mellitus insufficiently controlled with metformin.

Methods This was a randomized, double-blind, placebo-controlled, parallel-group, multi-centre study enrolling participants with Type 2 diabetes (n = 484) treated with metformin. Participants were randomized to receive either lixisenatide in a one-step dose increase or a two-step dose increase vs. placebo for 24 weeks, followed by a ≥ 52-week variable double blind period. Primary outcome was HbA_{1c} reduction at week 24.

Results Lixisenatide one-/two-step once daily significantly improved HbA_{1c} at week 24 compared with placebo ($P < 0.0001$) and allowed more participants to achieve $HbA_{1c} < 53$ mmol/mol (< 7.0%) ($P \leq 0.0005$). Improvements were observed in fasting plasma glucose (–0.5/–0.6 vs. +0.1 mmol/l; $P < 0.001$) and body weight (–2.6/–2.7 vs. –1.6 kg; $P < 0.005$). At week 24, adverse events were reported by 67.7/70.8/65.6% of participants treated with lixisenatide one-/two-step/placebo, respectively—nausea and vomiting being reported most frequently. Symptomatic hypoglycaemia occurred in 1.9/2.5% of participants on one-/two-step lixisenatide and 0.6% with placebo, with no severe episodes. Lixisenatide continued to be efficacious and well tolerated during the variable double-blind extension period of at least 52 weeks.

Conclusions Lixisenatide one- or two-step dose-increase regimens significantly improved glycaemic control and decreased body weight over 24 weeks and during a long-term extension period without increasing hypoglycaemia. The study confirmed that tolerability in the one-step group was at least similar to the two-step dose increase, with nausea/vomiting and hypoglycaemia frequency being lower in the one-step regimen.

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Introduction

Metformin is recommended as the first-line, glucose-lowering drug therapy of choice for many participants with Type 2 diabetes mellitus and provides a good basis for combination therapy when monotherapy alone becomes inadequate [1–3].

When lifestyle measures and metformin are no longer sufficient, adding a second drug with a patient-individualized approach of either a sulphonylurea, a thiazolidinedione, a dipeptidyl peptidase-4 (DPP-4) inhibitor, a glucagon-like peptide-1 (GLP-1) receptor agonist or an insulin regimen is recommended, and further treatment extension with another option should follow if treatment targets are not reached [4].

GLP-1 receptor agonists are one of the existing options for combination with metformin and—in addition to improved glycaemic control—are associated with beneficial effects on weight and a low propensity for hypoglycaemia [5]. Currently, four marketed GLP-1 receptor agonists are available with variable dosing options, including twice-daily and once-weekly formulations of exenatide and a once-daily formulation of liraglutide [5–9].

Lixisenatide is a once-daily prandial GLP-1 receptor agonist for the treatment of Type 2 diabetes that was granted marketing authorization by the European Medicines Agency in February 2013 [9–17]; it has distinct effects on

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What's new?

- Treatment with lixisenatide, when used in a one- or a two-step dose-increase regimen, led to a significant reduction compared with placebo in HbA_{1c} levels at week 24 and during the entire double-blind study period of at least 76 weeks.
- Tolerability of the one-step dose-increase regimen was at least as good as with the two-step dose-increase regimen.
- The efficacy and safety of lixisenatide in combination with metformin were confirmed during the main treatment period of 24 weeks and during the entire double-blind study period of at least ≥ 76 weeks.

postprandial blood glucose as a result of slowing down of gastric emptying [18]. Results from a 13-week dose-ranging study demonstrated that lixisenatide (5, 10, 20 or 30 μg once daily or twice daily) is effective in participants with Type 2 diabetes who have failed metformin monotherapy. Lixisenatide 20 μg once daily significantly improved HbA_{1c} compared with placebo, whilst reducing postprandial plasma glucose, and this dose provided the most favourable combined efficacy and gastrointestinal tolerability profile [10]. The significance of the once-daily prandial GLP-1 receptor agonist lixisenatide compared with other GLP-1 receptor agonists is its prandial nature, its use as a once-daily injection and its lower side-effect profile, while also providing rapid onset of action. This rapid onset may help to prevent tachyphylaxis, thereby maintaining the beneficial effect on gastric emptying delay and improving postprandial plasma glucose, while having a beneficial effect on body weight.

Here, we report the GetGoal-F1 study, which investigated the efficacy and safety of lixisenatide once daily as add-on therapy in participants with Type 2 diabetes insufficiently controlled on metformin monotherapy. Gastrointestinal side effects are associated with the GLP-1 receptor agonist drug class [5,6] and it has been shown that a stepwise dose increase improves tolerability. Therefore, two different regimens—a two-step and a simplified one-step dose-increase regimen—were tested in this study.

Research design and methods

This was a phase III, randomized, double-blind, placebo-controlled, four-arm, parallel-group, multi-centre, multinational study consisting of up to 2 weeks of screening and a 1-week placebo run-in, a main double-blind treatment period of 24 weeks (primary efficacy endpoint assessment), followed by a variable, controlled, double-blind extension period of at least 52 weeks. The study was conducted at 75 centres across 15 countries, approved by the institutional review boards or ethics committees, and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All participants provided written informed consent prior to study start. An independent Data Monitoring Committee supervised conduct of the study.

Participants

Men and women, aged 24–79 years, with Type 2 diabetes (≥ 1 year since diagnosis) currently receiving at least 1.5 g/day of metformin as monotherapy (for at least 3 months) and with HbA_{1c} 53–86 mmol/mol (7–10%), inclusive, were enrolled.

Main exclusion criteria included: use of injectable or oral glucose-lowering agents (other than metformin) within 3 months prior to the time of screening; fasting plasma glucose at screening > 13.9 mmol/l (250 mg/dl); history of unexplained pancreatitis, chronic pancreatitis, pancreatectomy, stomach/gastric surgery or inflammatory bowel disease.

Randomization and blinding

Participants were randomized in a 2:2:1:1 ratio to one of four treatment regimens administered subcutaneously within 1 h before the morning meal: (1) lixisenatide one-step dose increase (10 μg once daily for 2 weeks then 20 μg once daily; $n = 161$); (2) lixisenatide two-step dose increase (10 μg once daily for 1 week, 15 μg once daily for 1 week then 20 μg once daily; $n = 161$); (3) matching placebo one-step dose increase ($n = 82$); (4) matching placebo two-step dose increase ($n = 80$). The study was double blind with regard to active and placebo treatments; study drug volume was not blinded. Participants continued on their established metformin doses and were stratified by screening values of HbA_{1c} < 64 mmol/mol, ≥ 64 mmol/mol (< 8%, ≥ 8%) and BMI (< 30 kg/m^2, ≥ 30 kg/m^2).

Efficacy and safety assessments

The primary endpoint was the absolute change in HbA_{1c} from baseline to week 24. Analysis was based on the modified intent-to-treat population, comprising all randomized participants who received at least one dose of double-blind investigational product and had a baseline and at least one post-baseline assessment for any primary or secondary efficacy variable.

Secondary efficacy endpoints during the main treatment period included the percentage of participants reaching HbA_{1c} < 53 mmol/mol (< 7.0%) or ≤ 48 mmol/mol (≤ 6.5%), fasting plasma glucose, body weight and the percentage of participants receiving rescue therapy. Efficacy parameters were assessed descriptively during the extension period.

Safety and tolerability were assessed during the 24-week main treatment period and the entire double-blind treatment period (≥ 76 weeks) based on systematic adverse event and serious adverse event reporting and other specific safety

information. Potential allergic or allergic-like reactions that might be associated with the lixisenatide peptide were assessed by a blinded allergic reaction adjudication committee.

Statistical analyses

The primary endpoint was analysed using an analysis of covariance (ANCOVA) model, with treatment group, screening strata for HbA_{1c} and BMI, and country as fixed factors, and baseline HbA_{1c} as a covariate. The two placebo arms were included as separate treatment levels in the ANCOVA model, but were combined as one group when making comparisons using appropriate contrast. A stepwise testing procedure was applied—first, the lixisenatide two-step titration arm was compared with the combined placebo group (primary objective); if statistically significant, then the lixisenatide one-step titration arm was compared with the combined placebo group (secondary objective). The difference between each lixisenatide titration group and the combined placebo group, two-sided 95% confidence intervals and *P*-values were estimated within the ANCOVA framework. Continuous secondary efficacy variables were analysed in the modified intent-to-treat population by ANCOVA; categorical secondary efficacy variables were analysed using a Cochran–Mantel–Haenszel method stratified on randomization strata. Efficacy endpoints during the variable extension period were evaluated by descriptive statistics. Safety analysis was performed by descriptive comparison of the safety population, comprising all randomized participants exposed to at least one dose of the double-blind investigational product.

Results

Patient characteristics and disposition

Demographic and baseline characteristics were well matched between treatment groups (Table 1). Of 884 participants screened, 500 entered the run-in period and 484 were randomized to one of the treatment arms. Two participants who were randomized to the placebo groups did not receive any treatment and were excluded from the analysis. Most participants (91% lixisenatide one-step, 89% lixisenatide two-step, 94% placebo combined) completed the 24-week main treatment period; 81% in the lixisenatide one-step, 75% in the lixisenatide two-step and 80% in the placebo combined groups also completed the entire study period of ≥ 76 weeks (see also Supporting Information, Fig. S1). A high proportion of participants were receiving the maintenance dose of 20 μg once daily at the end of the titration and the entire study period.

Efficacy

HbA_{1c}

Lixisenatide either in a one-step or a two-step dose-increase regimen significantly reduced HbA_{1c} at week 24 vs. placebo. Mean (± SD) HbA_{1c} was reduced from 64 ± 9.6 mmol/mol (8.0 ± 0.9%) at baseline to 54 ± 9.3 mmol/mol (7.1 ± 0.9%) at week 24 with lixisenatide one-step [least squares mean change (± SE): –10 ± 1.1 mmol/mol (–0.9 ± 0.10%)], from 65 ± 9.7 mmol/mol (8.1 ± 0.9%) to 56 ± 10.9 mmol/mol (7.3 ± 1.0%) with lixisenatide two-step [least squares mean change: –9 ± 1.1 mmol/mol (–0.8 ± 0.1%)] and from 64 ± 9.1 mmol/mol (8.0 ± 0.8%) to 60 ± 10.1 mmol/mol (7.6 ± 0.9%) with placebo combined [least squares mean change: –5 ± 1.1 mmol/mol (–0.4 ± 0.1%)]. The least squares mean change difference vs. placebo was –5 mmol/mol (–0.5%) (95% CI –7.3 to –3.5 mmol/mol, 95% CI –0.7 to –0.3; $P < 0.0001$) for lixisenatide one-step and –5 mmol/mol (–0.4%) (95% CI –6.4 to –2.5 mmol/mol, 95% CI –0.6 to –0.2; $P < 0.0001$) for lixisenatide two-step. The HbA_{1c} targets of < 53 mmol/mol (< 7.0%) and ≤ 48 mmol/mol (≤ 6.5%) were both achieved by significantly more participants in both the lixisenatide one-step and two-step groups compared with the combined placebo group ($P < 0.001$ for both) (Fig. 1c).

Table 1 Demographic and baseline characteristics (safety population)

Demographic variable	Lixisenatide one-step (*n* = 161)	Lixisenatide two-step (*n* = 161)	Placebo combined (*n* = 160)
Sex (men/women), %	44/56	45/55	45/55
Race (Caucasian/Black/Asian/Other), %	88/1/8/4	91/1/7/1	93/1/6/1
Age, years (mean ± SD)	55.4 ± 8.9	54.6 ± 8.9	58.2 ± 9.8
Duration of diabetes, years (mean ± SD)	5.8 ± 3.9	6.0 ± 4.6	6.2 ± 4.7
Weight, kg (mean ± SD)	90.3 ± 19.0	88.0 ± 16.8	87.9 ± 17.3
BMI, kg/m^2 (mean ± SD)	33.0 ± 5.8	32.1 ± 4.8	32.4 ± 5.5
HbA_{1c}, mmol/mol (mean ± SD)	64.0 ± 9.6	65.0 ± 9.7	64.0 ± 9.1
HbA_{1c}, % (mean ± SD)	8.0 ± 0.9	8.1 ± 0.9	8.0 ± 0.8
Fasting plasma glucose, mmol/l (mean ± SD)	9.6 ± 2.0	9.5 ± 2.5	9.5 ± 2.0
Daily metformin dose, mg (mean ± SD)	1968 ± 404	2036 ± 427	1943 ± 399
Duration of metformin treatment, years (mean ± SD)	3.3 ± 2.6	3.7 ± 3.4	3.6 ± 3.1

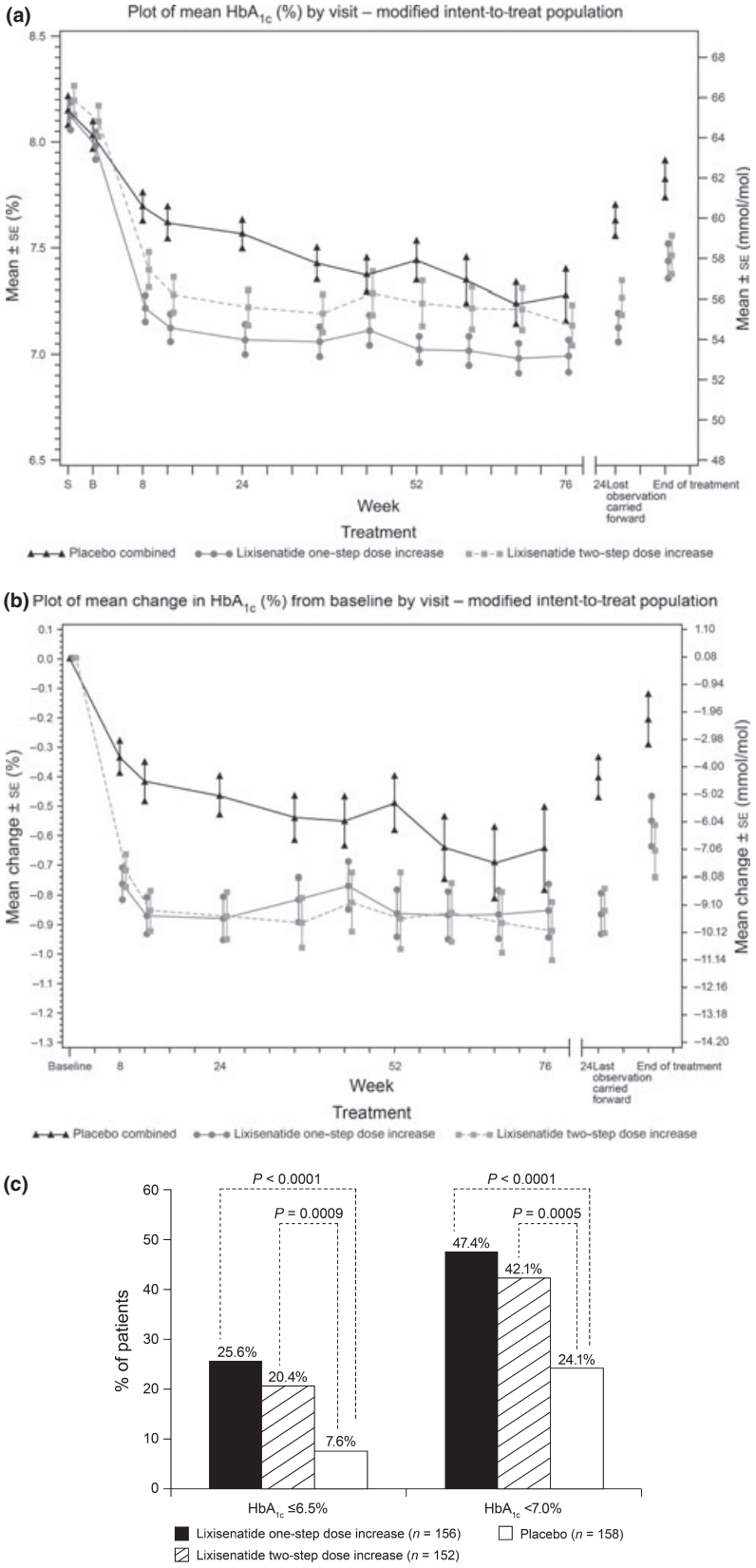

FIGURE 1 (a) Absolute HbA_{1c} values from baseline over entire study period and mean change from baseline HbA_{1c} values. (b) Mean change in HbA_{1c} from baseline over the entire study period with lixisenatide one-step dose-increase regimen, lixisenatide two-step dose-increase regimen and placebo. (c) Proportion of patients reaching HbA_{1c} targets at week 24.

Fasting plasma glucose

Both lixisenatide one- and two-step groups achieved significantly greater reductions in fasting plasma glucose at week 24 vs. the combined placebo group. Mean fasting plasma glucose was reduced from 9.6 ± 2.0 mmol/l at baseline to 8.4 ± 1.9 mmol/l at week 24 with lixisenatide one-step (least squares mean change: –0.5 ± 0.2 mmol/l), from 9.5 ± 2.5 to 8.4 ± 2.1 mmol/l with lixisenatide two-step (least squares mean change: –0.6 ± 0.2 mmol/l) and from 9.5 ± 2.0 to 9.1 ± 2.0 mmol/l with placebo combined (least squares mean change: +0.1 ± 0.2 mmol/l). The least squares mean difference vs. placebo was –0.7 mmol/l (95% CI –1.0 to –0.3; $P < 0.001$) for lixisenatide one-step and –0.7 mmol/l (95% CI –1.0 to –0.3; $P < 0.001$) for lixisenatide two-step groups.

Body weight

Absolute body weight values from baseline over the entire study period show that lixisenatide provided a significant reduction in body weight compared with placebo in both dose increase groups (Fig. 2). Mean body weight was reduced from 90.3 ± 19.0 kg at baseline to 87.7 ± 18.7 kg at week 24 [last observation carried forward (LOCF)] with lixisenatide one-step (least squares mean change: –2.6 ± 0.4 kg), from 88.1 ± 16.8 to 85.4 ± 16.8 kg with lixisenatide two-step (least squares mean change: –2.7 ± 0.4 kg), and from 87.9 ± 17.3 to 86.3 ± 17.4 kg with placebo combined (least squares mean change: –1.6 ± 0.4 kg) at 24 weeks (LOCF). The least squares mean difference vs. placebo was approximately –1.0 and –1.1 kg for the lixisenatide one- and two-step groups, respectively ($P < 0.01$).

Rescue therapy

The proportions of participants requiring rescue therapy during the 24-week main treatment period were 1.3% ($n = 2$) and 3.1% ($n = 5$) for the lixisenatide one- and two-step groups, respectively, and 4.4% ($n = 7$) for the combined placebo group.

Efficacy during the variable extension period

The efficacy of lixisenatide on glycaemic control was maintained during the variable extension period. At week 76, mean HbA_{1c} was reduced from baseline by –10 ± 9.8 mmol/mol (–0.9 ± 0.9%) for lixisenatide one-step and –10 ± 10.9 mmol/mol (–0.9 ± 1.0%) for lixisenatide two-step vs. –7 ± 14.2 mmol/mol (–0.6 ± 1.3%) for the combined placebo (Fig. 1b). The proportion of participants achieving HbA_{1c} targets of < 53 mmol/mol (< 7%) and ≤ 48 mmol/mol (≤ 6.5%) were 53.5 and 34.3% for lixisenatide one-step, 49.5 and 25.7% for lixisenatide two-step, and 41.8 and 22.8% for the combined placebo, respectively. Mean changes in fasting plasma glucose at week 76 were –1.3 ± 2.0, –1.0 ± 2.5 and –0.4 ± 2.8 mmol/l for lixisenatide one-step, two-step and combined placebo, respectively. Mean changes in body weight at week 76 were –3.8 ± 5.0, –3.4 ± 4.0 and –2.8 ± 4.6 kg for lixisenatide one-step, two-step and combined placebo, respectively.

Safety and tolerability

Lixisenatide was well tolerated during the study. The overall incidence of adverse events and serious adverse events at both week 24 and at the end of the entire double-blind treatment period (≥ 76 weeks) was similar in the two lixisenatide dose-increase groups and the placebo group (Table 2). The most common adverse events in the lixisenatide groups were gastrointestinal in nature, mainly mild or moderate nausea and vomiting. Fewer gastrointestinal adverse events were seen in the one-step lixisenatide group at 24 weeks [67 (41.6%)] than in the two-step lixisenatide group [76 (47.2%)] (Table 2). Nausea and vomiting occurred mainly during the first 3–4 weeks of treatment (reaching the rate of placebo from week 8 onwards) and did not lead to treatment discontinuation in most participants [at week 24, discontinuation due to nausea or vomiting was reported in lixisenatide one-step: 6 (3.7%); lixisenatide two-step: 7 (4.3%); combined placebo: 0]. No correlation was found between the occurrence of nausea or vomiting and weight loss.

During the entire treatment period, adverse events that were adjudicated as an allergic reaction were reported in 2.8% ($n = 9$) of lixisenatide-treated participants and in 3.8% ($n = 6$) of placebo-treated participants; two of these (0.6%; $n = 1$ in each lixisenatide dose-increase group) were adjudicated as possibly related to treatment. One was reported as allergic dermatitis after 5.5 months of treatment; the other was a serious allergic exanthema on the first day of lixisenatide treatment. Both were adjudicated as anaphylactic reactions by the Allergic Reaction Assessment Committee.

The overall incidence of symptomatic hypoglycaemia at week 24 was 1.9 and 2.5% in the lixisenatide one-step and two-step groups, respectively, compared with 0.6% for the placebo group (Table 2). Over the entire treatment period, symptomatic hypoglycaemia occurred in fewer lixisenatide one-step participants (3.7%) than in placebo and two-step participants (7.5% each). No severe hypoglycaemic events were reported.

Over the entire study period, nine participants (5.6%) in each lixisenatide titration group and three participants (1.9%) in the combined placebo group had injection-site reactions. None were serious or considered to be severe in intensity by the investigator, or led to treatment discontinuation (Table 2).

Throughout the entire study period, few participants reported a protocol pre-specified increase in pancreatic enzymes (amylase and/or lipase) in any treatment arm [four each in one-step (2.5%) and two-step (2.5%) lixisenatide participants and five in placebo participants (3.1%)]. No cases of confirmed pancreatitis were observed. Three participants reported a pre-specified event attributable to an increase in calcitonin levels ≥ 20 ng/l, along with an adverse

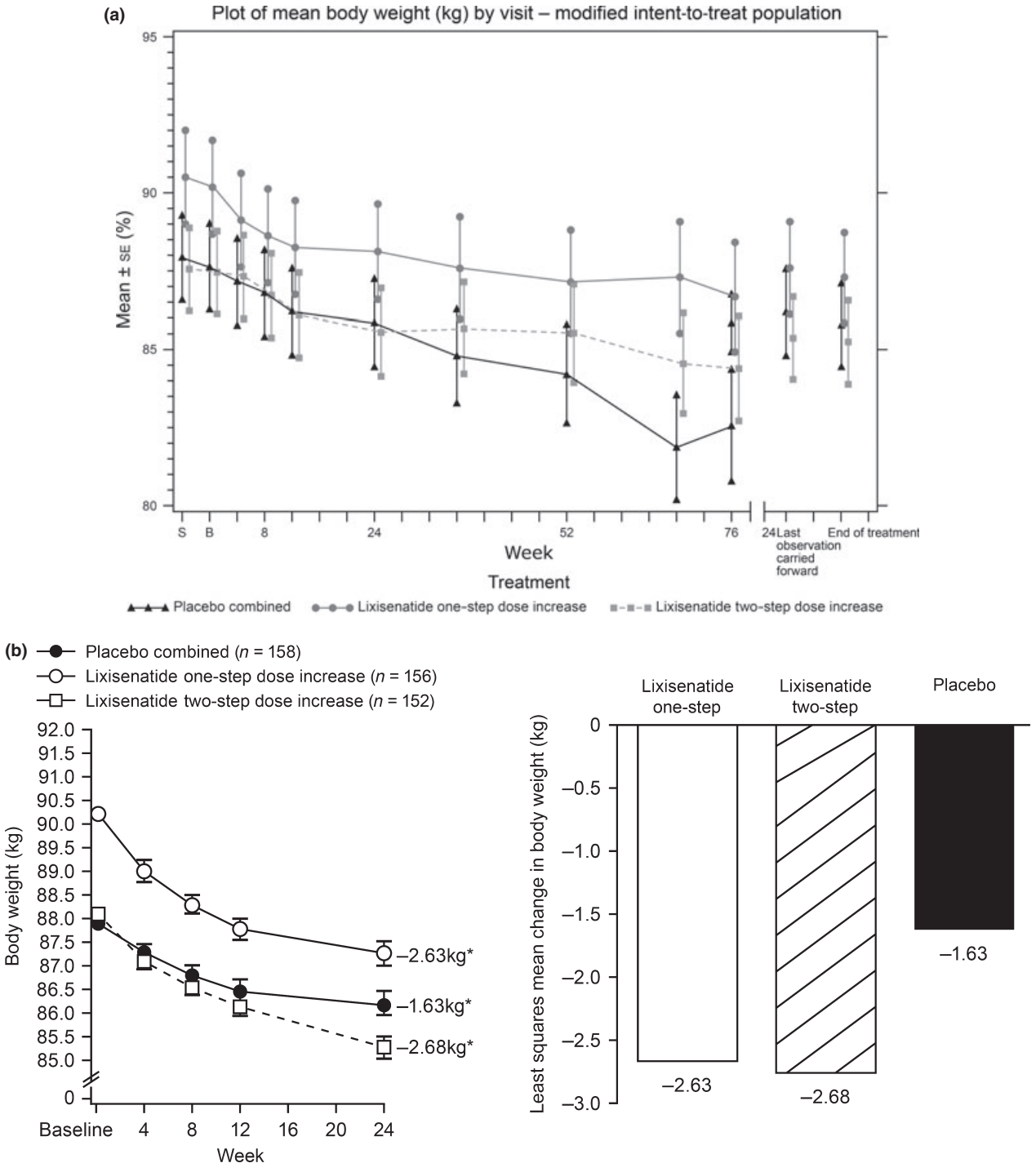

FIGURE 2 (a) Absolute body weight values from baseline over entire study period. (b) Least squares mean change in body weight over entire study period with lixisenatide one-step dose-increase regimen, lixisenatide two-step dose-increase regimen and placebo, with zero suppressed. *Least squares mean change at week 24.

event; one (0.6%) participant reported that 'calcitonin increased' in each of the one-step and the two-step groups, and one participant in the placebo group (0.6%) was diagnosed with medullary thyroid cancer during the study. This event was pre-existing at study entry, but was not diagnosed at that point; it was assessed as being unrelated to the investigational product by the investigator. Analysis of safety laboratory and electrocardiogram data did not reveal any specific safety signals.

Discussion

In this placebo-controlled study, lixisenatide 20 μg once daily, used in either a one- or two-step dose-increase regimen,

Table 2 Adverse events at week 24 and during the entire treatment period of ≥ 76 weeks (safety population)

Type of adverse event	Lixisenatide one-step (n = 161) n (%)	Lixisenatide two-step (n = 161)	Placebo combined (n = 160)
Any adverse event			
Week 24	109 (67.7)	114 (70.8)	105 (65.6)
Entire double-blind treatment	138 (85.7)	141 (87.6)	138 (86.3)
Any serious adverse event			
Week 24	5 (3.1)	7 (4.3)	4 (2.5)
Entire double-blind treatment	16 (9.9)	21 (13.0)	22 (13.8)
Death			
Week 24	1 (0.6)	0	0
Entire double-blind treatment	2 (1.2)	1 (0.6)	2 (1.3)
Discontinuation due to adverse events			
Week 24	9 (5.6)	13 (8.1)	4 (2.5)
Entire double-blind treatment	14 (8.7)	19 (11.8)	9 (5.6)
Gastrointestinal adverse events			
Gastrointestinal disorders (any)			
Week 24	67 (41.6)	76 (47.2)	35 (21.9)
Entire double-blind treatment	83 (51.6)	90 (55.9)	50 (31.3)
Nausea			
Week 24	42 (26.1)	57 (35.4)	7 (4.4)
Entire double-blind treatment	47 (29.2)	62 (38.5)	13 (8.1)
Vomiting			
Week 24	19 (11.8)	25 (15.5)	0
Entire double-blind treatment	21 (13.0)	29 (18.0)	1 (0.6)
Diarrhoea			
Week 24	10 (6.2)	20 (12.4)	14 (8.8)
Entire double-blind treatment	16 (9.9)	24 (14.9)	21 (13.1)
Symptomatic hypoglycaemia*			
Week 24	3 (1.9)	4 (2.5)	1 (0.6)
Entire double-blind treatment	6 (3.7)	12 (7.5)	12 (7.5)
Severe hypoglycaemia†	0	0	0
Injection-site reactions			
Week 24	7 (4.3)	7 (4.3)	2 (1.3)
Entire double-blind treatment	9 (5.6)	9 (5.6)	3 (1.9)

*Symptomatic hypoglycaemia—event with clinical symptoms with either plasma glucose < 60 mg/dl or prompt recovery after oral carbohydrate administration (if no plasma glucose measurement was available), intravenous glucose or glucagon administration.
†Severe hypoglycaemia—event with clinical symptoms considered to result from hypoglycaemia in which the participant required the assistance of another person, because the participant could not treat him/herself as a result of acute neurological impairment directly resulting from the hypoglycaemic event, and one of the following: event was associated with plasma glucose < 2.0 mmol/l (36 mg/dl); if no plasma glucose measurement is available, then the event was associated with prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration.

significantly improved glycaemic control at week 24 in participants with Type 2 diabetes insufficiently controlled on metformin. There were significantly greater decreases in HbA_{1c} with lixisenatide one-step and lixisenatide two-step dose-increase regimens vs. placebo, and significantly more lixisenatide-treated participants (both dose-increase regimens) achieved HbA_{1c} targets of ≤ 48 mmol/mol (≤ 6.5%) and < 53 mmol/mol (< 7.0%) than placebo. Lixisenatide also significantly reduced body weight compared with placebo. The long-term extension data, ≥ 76 weeks, demonstrated that the efficacy of lixisenatide on glycaemic control was maintained, with sustained reductions in body weight until the end of the entire treatment period.

The magnitude of the HbA_{1c} reductions from baseline and final achieved HbA_{1c} values reported here were of a similar range to those reported with other GLP-1 receptor agonists (exenatide 10 μg twice daily or liraglutide 1.2/1.8 mg once daily) as an add on to metformin monotherapy [19–21]. Studies to date have shown improvements ranging from –16.4 to –8.7 mmol/mol (–0.8 to –1.5%) [from baseline values of 66–68 mmol/mol [8.2–8.4%)] and final HbA_{1c} values in the range of 53–57 mmol/mol (7.0–7.4%) [19–21]. However, it should be noted that HbA_{1c} improvements in the present study occurred in the context of slightly better baseline glycaemic control ~64 mmol/mol (~8.0%) and was sustained during the variable long-term extension of the study.

Overall, lixisenatide was well tolerated during the entire treatment period. Approximately 90% of participants in the lixisenatide and placebo groups completed the 24-week main treatment period and > 75% of participants completed the entire study period of at least 76 weeks. Importantly, the addition of lixisenatide to metformin monotherapy was associated with a low occurrence of symptomatic hypoglycaemic events (≤ 2.5%) at week 24. Over the entire double-blind study period, the percentage of participants experiencing hypoglycaemia in either of the lixisenatide groups did not exceed that seen with placebo (7.5%); no severe hypoglycaemic events were reported.

As expected, and in common with other GLP-1 receptor agonists [5], the most frequent adverse events associated with lixisenatide were gastrointestinal related. Approximately 30% of participants experienced nausea over 24 weeks, which is broadly consistent with other studies of GLP-1 receptor agonists used as an add on to metformin-based therapy, for which frequency ranges widely from 15 to 50% [5,19–21]. In the GetGoal-Mono study [12], nausea frequency (22% for the combined lixisenatide groups) is consistent with that observed in the lixisenatide dose-ranging study (25.5% with 20 μg once daily dose) and in studies conducted with other GLP-1 receptor agonists when used in monotherapy (13–29%) [22,23].

GLP-1 receptor agonists avoid some of the potential tolerability issues that may be associated with other glucose-lowering agents that are frequently used in the second-line setting, including increased risk of hypoglycaemia (potential issue with sulphonylureas and insulin therapy) and weight gain (potential issue with sulphonylureas,

insulin therapy and thiazolidinediones) [5,24,25]. The best choice of GLP-1 receptor agonist in this setting will also depend on the individual requirements of participants, based on the overall efficacy/tolerability profile and optimal/preferred dosing frequency. In this study, we have shown that lixisenatide can provide an effective once-daily option in participants unable to control their diabetes with metformin monotherapy, with significant improvements in both HbA_{1c} and fasting plasma glucose, accompanied by significant weight loss compared with placebo, and a low propensity for hypoglycaemia. Although not measured here, previous data have shown that lixisenatide markedly improves postprandial plasma glucose control after a breakfast meal test and may thus represent a valuable option for targeting postprandial hyperglycaemia [9,11,12,26]. Indeed, lixisenatide is the first once-daily prandial GLP-1 receptor agonist with a predominantly prandial glucose-lowering effect that has been indicated for use as an add on to basal insulin and in combination with oral glucose-lowering agents.

This study confirms that one- and two-step lixisenatide dose-increase regimens are generally comparable with respect to efficacy and tolerability, supporting a role for once-daily lixisenatide monotherapy using a one-step dose-increase regimen. The frequency of nausea/vomiting and hypoglycaemia appeared slightly lower, and HbA_{1c} reductions slightly greater, with the one-step regimen. This finding is consistent with a 12-week, phase III study of lixisenatide monotherapy in participants not receiving any glucose-lowering drugs therapy (GetGoal-Mono study) [12]. That study also found that there was a trend towards less nausea/vomiting and hypoglycaemia and greater HbA_{1c} lowering with the one-step regimen. The data from the GetGoal-F1 study, together with data from GetGoal-Mono [12], allow for the selection of the simplified one-step regimen for initiation of lixisenatide treatment. A one-step dose-increase regimen (i.e. 10 μg once daily for 2 weeks followed by 20 μg once daily) should be simpler to implement for participants and physicians, who can be confident that it can be used with at least equivalent efficacy, gastrointestinaly tolerability and propensity for hypoglycaemia, as with the two-step dose-increase regimen.

Conclusions

In participants with Type 2 diabetes uncontrolled on metformin, add-on treatment with the once-daily prandial GLP-1 receptor agonist lixisenatide, given in either a one- or two-step dose-increase regimen, significantly improved glycaemic control and decreased body weight with no increased risk of hypoglycaemia. There was no increased risk of hypoglycaemic events with lixisenatide vs. placebo over the long term, and the one-step regimen was at least comparable with the two-step regimen in terms of both efficacy and tolerability. The trend toward lower levels of gastrointestinal side effects in the one-step regimen compared with the two-step regimen means that it is a simpler and more convenient regimen for both participants and physicians.

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Competing interests

GBB has received honoraria for consulting, lecturing and advising from Sanofi, Eli Lilly, Novartis, Becton & Dickinson. MM has received honoraria for consulting, lecturing and advising from AstraZeneca, Novartis, Merck Sharp & Dohme, Mitsubishi Tanabe, NovoNordisk, Sanofi. MH has received speaker honoraria from Takeda, GlaxoSmithKline, Roche, Bayer, Lilly, Sanofi-Aventis; and advisory board honoraria from Sanofi-Aventis, Takeda, Bristol-Myers Squibb and GlaxoSmithKline. EN, GB and YW are employees of Sanofi. SD has nothing to declare.

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Previous presentations

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Subject disposition.