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Lixisenatide, a novel GLP-1 receptor agonist: efficacy, safety and clinical implications for type 2 diabetes mellitus

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Recent advances in therapies for the treatment of type 2 diabetes mellitus (T2DM) have led to the development of glucagon-like peptide-1 receptor agonists (GLP-1 RAs), which, unlike insulin and sulphonylurea, are effective, with a low risk of hypoglycaemia. Lixisenatide is recommended as a once-daily GLP-1 RA for the treatment of T2DM. In persons with T2DM, lixisenatide 20 μg once-daily given by bolus subcutaneous injection improves insulin secretion and suppresses glucagon secretion in a glucose-dependent manner. Compared with the longer-acting GLP-1 RA liraglutide, lixisenatide achieved a significantly greater reduction in postprandial plasma glucose (PPG) during a standardized test breakfast in persons with T2DM otherwise insufficiently controlled on metformin alone. This is primarily due to the greater inhibition of gastric motility by lixisenatide compared with liraglutide. The efficacy and safety of lixisenatide was evaluated across a spectrum of T2DM in a series of phase III, randomized, placebo-controlled trials known as the GetGoal programme. Lixisenatide monotherapy or as add-on to oral antidiabetic agents or basal insulin achieved significant reductions in glycated haemoglobin, PPG and fasting plasma glucose, with either weight loss or no weight gain. The most frequent adverse events were gastrointestinal and transient in nature. Lixisenatide provides an easy, once-daily, single-dose, add-on treatment to oral antidiabetic agents or basal insulin for the management of T2DM, with little or no increased risk of hypoglycaemia and a potential beneficial effect on body weight.

Keywords: diabetes mellitus, GLP-1

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Introduction

Despite substantial advances over the past decades in the management of hyperglycaemia in type 2 diabetes mellitus (T2DM), many glucose-lowering therapies either fail to achieve and/or fail to maintain adequate glycaemic control in the long term due to the progressive nature of the disease [1,2]. Achieving an optimal response may also be limited by adverse effects such as hypoglycaemia, weight gain and gastrointestinal (GI) intolerance [1]. Consequently, there is a continuing need to develop more effective and better-tolerated glucose-lowering therapies that can both achieve and sustain near normoglycaemia by focusing on β-cell preservation to prevent or retard disease progression.

The Incretin System

The incretin system plays a key role in the maintenance of glucose homeostasis, predominantly via both the promotion of insulin secretion and inhibition of glucagon secretion. The incretin hormones include glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), both of which are rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP4) [3–6]. GLP-1 receptors are found not only in the pancreas and the GI tract, but also in the brain, the vascular system, the heart and the kidney (Figure 1) [3,7].

In recent years, GLP-1 receptor agonists (GLP-1 RAs), incretins, have shown promise as an important therapeutic option in the management of T2DM [8]. The incretin system has therefore provided an attractive opportunity for the development of innovative therapies for T2DM, as it has multiple and complex glucose and weight-regulating actions, which are due to the combination of enhanced insulin secretion and suppression of glucagon secretion, delayed gastric emptying and promotion of satiety [9–17]. In contrast to other secretagogues, including sulphonylurea and meglitinide hypoglycaemic agents, native GLP-1 and GLP-1 mimetics enhance insulin secretion in a glucose-dependent manner [18] and therefore have a low propensity to cause hypoglycaemia. In addition, preclinical studies using *in vitro* and animal models have suggested that GLP-1 RAs have the potential to preserve pancreatic islet β-cells by enhancing proliferation while inhibiting apoptosis, which has the potential to contribute to a more stable metabolic control in the longer term [19]. Through their action in delaying gastric emptying and increasing satiety, GLP-1 RAs reduce overall energy intake and therefore can result in weight loss. Other potential effects include cardioprotection and neuroprotection [20–22]. In addition, a number of studies have also reported that GLP-1 RAs reduced cardiovascular risk possibly through improvements in lipid profiles [23–25] and a reduction in both systolic blood

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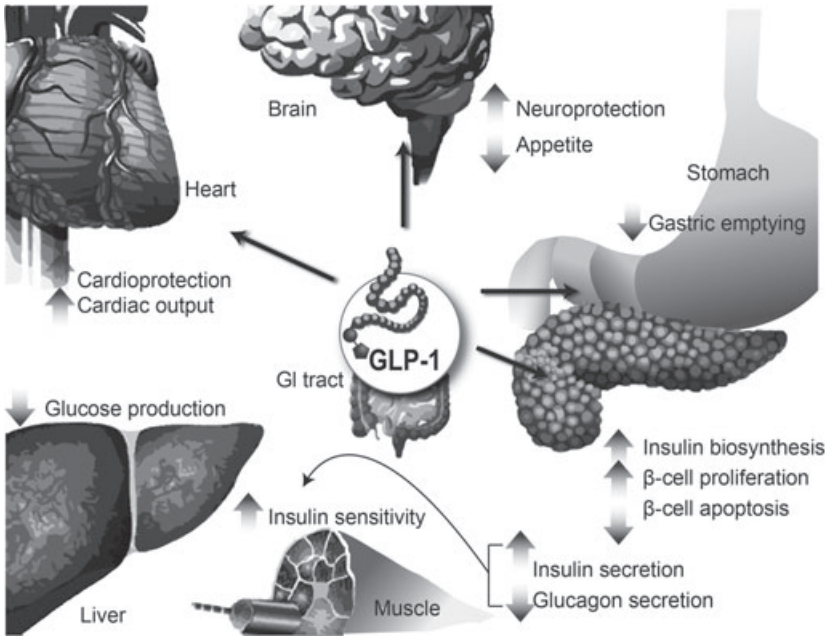

Figure 1. The effects of GLP-1 in multiple body systems. GI, gastrointestinal; GLP-1, glucagon-like peptide-1. Adapted with permission from Ref. [3] from Elsevier.

pressure and cardiac events such as dysrhythmias, heart failure and myocardial infarction [26–30]. The diverse actions of this therapeutic class make GLP-1 RAs an appealing addition to the current options for treating T2DM. These agents are being increasingly incorporated into diabetes treatment algorithms as second- or third-line options as add-ons to other antidiabetic therapies [1,31].

Currently Approved GLP-1 RAs

Four GLP-1 RAs are currently approved for the treatment of T2DM – exenatide (Byetta®, Bristol-Myers Squibb–AstraZeneca, Uxbridge, UK), exenatide once-weekly (Bydureon®, Bristol-Myers Squibb–AstraZeneca) liraglutide (Victoza®, Novo Nordisk, Bagsvaerd, Denmark) and lixisenatide (Lyxumia®, Sanofi, Paris, France). Exenatide is a synthetic form of exendin-4, a 39-amino-acid peptide isolated from the salivary secretion of the Gila monster lizard [32], which has a mean terminal half-life of 2.4 h (Figure 2). Exenatide (Byetta) was approved in Europe in 2006, for subcutaneous injection twice daily, preferably 30–60 min before the first and last meal of the day. Exenatide is also available in an extended-release formulation (Bydureon) suitable for once-weekly administration [33]. Liraglutide (Victoza) is an acylated analogue of GLP-1, with approximately 97% amino-acid sequence homology to endogenous GLP-1 and approved in Europe in 2009 (Figure 2). Liraglutide has a half-life of approximately 11–15 h in healthy individuals [34,35] and is advocated for once-daily administration at any time of the day, independent of meal times. Exenatide and liraglutide have been shown to lower glycated haemoglobin (HbA1c) by approximately 1 and 1–2%, respectively, both with associated weight loss of around 1–3 kg, and the main tolerability issue is transient nausea, which rarely leads to drug discontinuation [36]. Interestingly, although exenatide and liraglutide share the same basic mechanisms of action, differences in their pharmacokinetic profiles translate into differential effects on fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) levels [9]. This was first demonstrated in a 26-week, randomized, open-label, parallel-group, multi-national study in adults with inadequately controlled T2DM who were assigned to receive, in addition to their current therapy, liraglutide 1.8 mg once-daily ($n = 233$) or exenatide 10 μg twice-daily ($n = 231$) [30]. Liraglutide lowered the mean FPG more than exenatide (−1.61 vs. −0.60 mmol/l; estimated treatment difference −1.01 mmol/l, $p < 0.0001$). In contrast, exenatide reduced the PPG increment more than liraglutide following both breakfast and evening meal (breakfast: estimated treatment difference 1.33 mmol/l, $p < 0.0001$ and evening meal: estimated treatment difference 1.01 mmol/l, $p = 0.0005$) [30]. The greater effect of exenatide versus liraglutide on PPG control has been interpreted as exenatide possessing a greater inhibitory effect on gastric emptying due to its short duration of action, which is in contrast to that of the longer-acting liraglutide [37]. The differential efficacy of short- and long-acting GLP-1 RAs on PPG control appears to be related to differences in their pharmacokinetic profile [38]. Studies suggest that agents with a longer half-life undergo tachyphylaxis of any initial gastric inhibitory effect, whereas agents with a shorter half-life such as exenatide do not undergo this phenomenon and retain their effect on gastric empting even after repeated exposure [35,38,39]. As basal insulin therapy predominantly targets FPG, and short-acting GLP-1 RAs predominantly target PPG (by slowing gastric emptying), the addition of a short-acting GLP-1 RA to basal insulin has the potential to further improve overall glycaemic control.

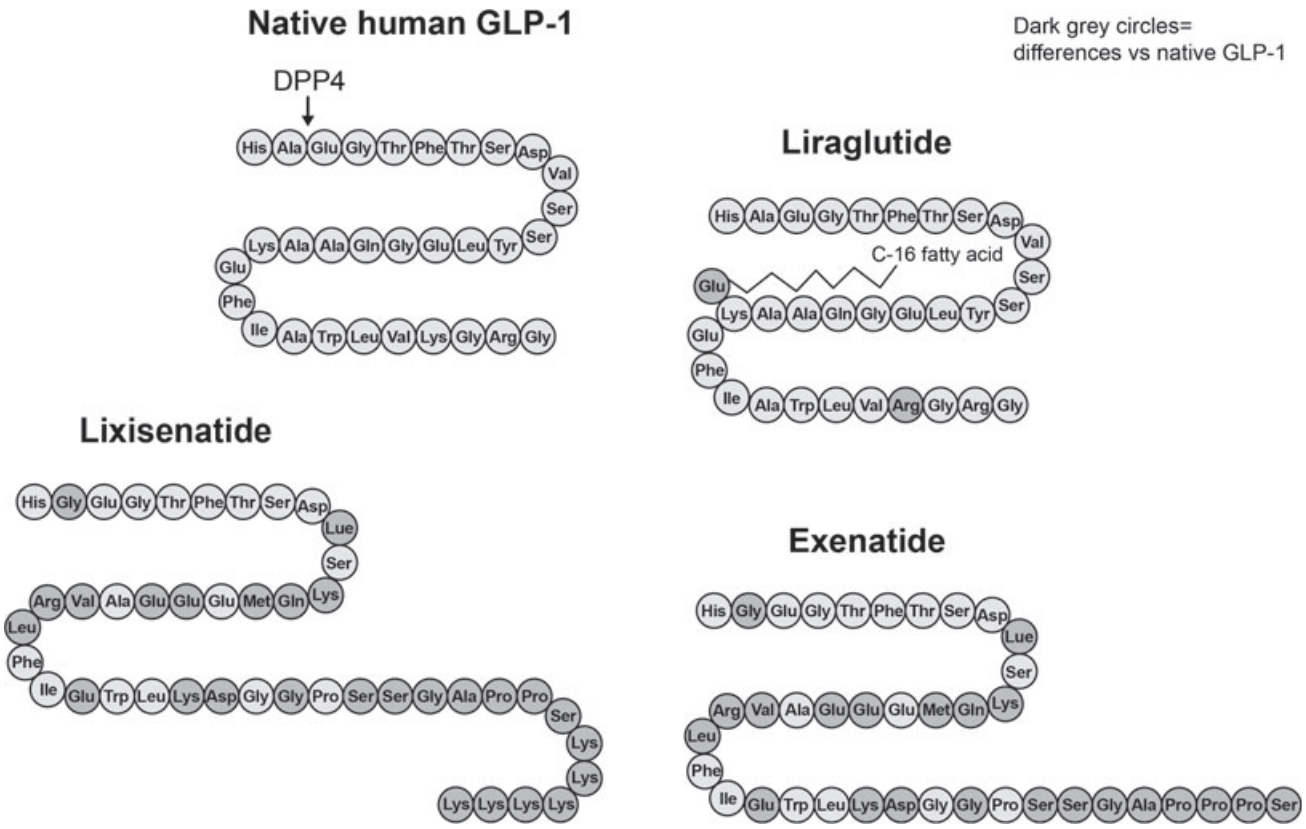

Figure 2. Structure of GLP-1 agonists. DPP4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1.

The Development of Lixisenatide

Lixisenatide is a once-daily prandial GLP-1 RA for the treatment of adults with T2DM [40]. Lixisenatide is a 44-amino-acid peptide that is amidated at the C-terminal amino acid and shares some structural elements with exendin-4 (Figure 2). The phase III clinical trial programme for lixisenatide, known as the GetGoal programme, began in 2008 and has enroled more than 5000 people with T2DM globally. This extensive programme has been designed to assess the efficacy and safety of lixisenatide given once-daily across the spectrum of T2DM, either as monotherapy or in combination with commonly used antidiabetic agents (metformin, sulphonylureas or thiazolidinedines) in a series of randomized controlled trials. Additionally, three studies in the GetGoal programme have investigated the combined effects of lixisenatide and basal insulin [40–43]. The rationale for such a combination is based on evidence that lixisenatide (and other short-acting GLP-1 RAs) target PPG (with a low risk of hypoglycaemia and beneficial weight loss), whereas basal insulin primarily targets FPG. It has been demonstrated that the combined use of short-acting (prandial) GLP-1 RAs and long-acting basal insulins provide complementary effects on glycaemic control [40–42, 44, 45]. In addition, preclinical studies have indicated that the combination of GLP-1 RAs and insulin analogues offers protection for pancreatic β-cells against cytokine and fatty-acid-induced apoptosis [46]. Theoretically, the shorter-acting GLP-1 RAs by virtue of their superior postprandial glycaemic control [30,38], compared with GLP-1 RAs with a prolonged duration of action (with predominant effect in the fasting, non-prandial), should be more effective in combination with basal insulin. However, only a head-to-head study comparing short- and long-acting GLP-1 RAs added to basal insulin will answer this question.

The objective of this article is to present both the pharmacological profile of lixisenatide and an overview of the currently available clinical experience with lixisenatide from its phase III clinical trial programme.

Pharmacological Profile of Lixisenatide

After multiple dose administration in subjects with T2DM, the mean terminal half-life was approximately 3 h, with a mean apparent clearance (CL/F) of about 35 l/h.

On the basis of early pharmacodynamic studies, however, as its clearance is lowered by approximately 30% in those with severe renal impairment (glomerular filtration rate of <30 ml/min), dosage adjustment may be required in this population [47,48]. Lixisenatide can, however, be used in individuals with mild-to-moderate renal impairment without dose adjustment; this information does not substitute any prescribing information that is or will be made available for lixisenatide. Several studies have demonstrated significant improvements in overall HbA1c, PPG and FPG [48–52]. Pharmacodynamic data demonstrate that lixisenatide can restore the early-phase insulin response to intravenous glucose, decrease glucagon secretion, enhance systemic glucose disposal and retard gastric

emptying. It can delay meal-derived glucose absorption without evidence of tachyphylaxis [53–55]. All these effects concur to improve blood glucose control with lixisenatide.

Lixisenatide Restores Insulin Secretion and Accelerates Glucose Disposal

The effect of lixisenatide 20 µg on insulin release and glucose disposal has been assessed in two placebo-controlled, single-dose, crossover studies in which people without diabetes and people with early-stage T2DM received lixisenatide 20 µg or matching placebo 2 h prior to an intravenous glucose challenge [54,55].

The first study investigated the insulin response to lixisenatide in 20 non-diabetic subjects [54]. Lixisenatide enhanced the first-phase insulin secretion [insulin area under the curve (AUC) in the first 10 min] by 2.4-fold [90% confidence interval (CI): 2.1–2.6], whereas the second-phase insulin release (insulin AUC within 10–120 min) remained essentially unchanged [0.9-fold (90% CI: 0.8–1.0)]. Glucose disposal was enhanced by 2.3-fold (90% CI: 1.9–3.0). No impairment of the glucagon counter-regulatory response was observed [54].

The second study compared insulin secretion and glucose disposal following the administration of lixisenatide in people with early-stage T2DM (n = 22) and non-diabetic healthy subjects during an intravenous glucose challenge (n = 20) [55]. Insulin secretion rates (based on C-peptide levels) were used to determine the first-phase ($AUC_{0-10\,min}$) and second-phase ($AUC_{10-120\,min}$) β-cell response. Insulin, C-peptide and glucagon concentration–time curves and glucose disposal rates (K_{glu}) were determined over 2 h. Lixisenatide enhanced the first-phase insulin secretory response in subjects with T2DM to levels seen in healthy subjects on placebo (Figure 3).

The second-phase insulin response was greater and elevated for more than 2 h in those with T2DM receiving lixisenatide compared with placebo. The glucose disposal rate (K_{glu} value) was enhanced by twofold following lixisenatide administration. Overall, a single dose of lixisenatide 20 µg quantitatively restored the early-phase insulin release to intravenous glucose in people with early T2DM and enhanced the second-phase response accompanied by enhanced glucose disposal without impairing counter-regulation by glucagon [56].

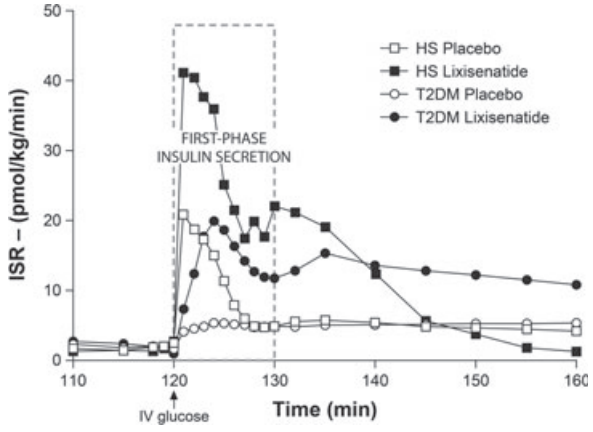

Figure 3. Effect of lixisenatide on first-phase insulin secretion in healthy subjects and patients with T2DM. Intravenous injection of glucose at 120 min (0.3 g/kg over 30 s). Subcutaneous injection of lixisenatide 20 µg at time 0. HS, healthy subjects; ISR, insulin secretion rate; T2DM, type 2 diabetes mellitus [55].

Lixisenatide Reduces PPG and Slows Gastric Emptying

The effects of lixisenatide on gastric emptying and PPG were evaluated in a randomized, 28-day trial in which lixisenatide was injected subcutaneously using an ascending dose range (5–20 µg increased at 4-day intervals in increments of 2.5 µg) in persons with T2DM on metformin ± sulphonylurea. Blood glucose was determined before and after three standardized meals (breakfast, lunch and dinner). Lixisenatide 20 µg once-daily produced significant reductions versus placebo in PPG AUC after breakfast, lunch and dinner [53]. To determine the effects of lixisenatide on gastric emptying and PPG, gastric emptying was determined by a ^{13}C-octanoic acid breath test after a standardized breakfast at baseline and at day 28. A total of 21 and 22 people were randomized to lixisenatide once-daily and placebo, respectively. With lixisenatide 20 µg once-daily, there was a reduction in PPG when compared with placebo after either breakfast ($p < 0.0001$), lunch ($p < 0.001$) or dinner ($p < 0.05$) (Figure 4). The duration of gastric emptying (50% emptying time) assessed after breakfast increased substantially from baseline with lixisenatide 20 µg but not with placebo (change from baseline ± s.d.: −24.1 ± 133.1 min for placebo and 211.5 ± 278.5 min for lixisenatide; $p < 0.01$). There was an inverse relationship between PPG–AUC and gastric emptying with lixisenatide 20 µg ($n = 17$, $r^2 = 0.51$, $p < 0.05$), but not with placebo. Overall, lixisenatide 20 µg once-daily reduced postprandial glycaemic excursions in people with T2DM, as a result of delayed gastric emptying [53].

The short-acting profile of lixisenatide may be expected to result in a more significant inhibition of gastric emptying versus long-acting liraglutide. In a study comparing the effect of lixisenatide and liraglutide on gastric emptying in Wistar rats, lixisenatide produced a marked and dose-dependent decrease in the rate of gastric emptying at all doses studied (1–10 µg/kg) when using a liquid test meal. The effect was greater with lixisenatide than liraglutide, even at the highest studied dose of liraglutide (1000 mg/kg) [57]. Similarly, when comparing short-acting exenatide IR and liraglutide in rats, both produced reductions in gastric emptying, although the effect with liraglutide was markedly diminished after 14 days, suggesting the presence of tachyphylaxis due to continuous exposure to the longer-acting GLP-1 RA [38]. There is an ongoing, randomized, open-label, phase II/III trial in persons with T2DM treated with insulin glargine comparing the effect of lixisenatide and liraglutide on PPG after a standardized breakfast as a primary outcome and the effect on gastric emptying as a secondary outcome.

Lixisenatide Once-Daily Has a Significantly Greater PPG-Lowering Effect Than Liraglutide Once-Daily

The impact on PPG of lixisenatide 20 µg once-daily (n = 77) was compared with liraglutide 1.8 mg once-daily (n = 71)

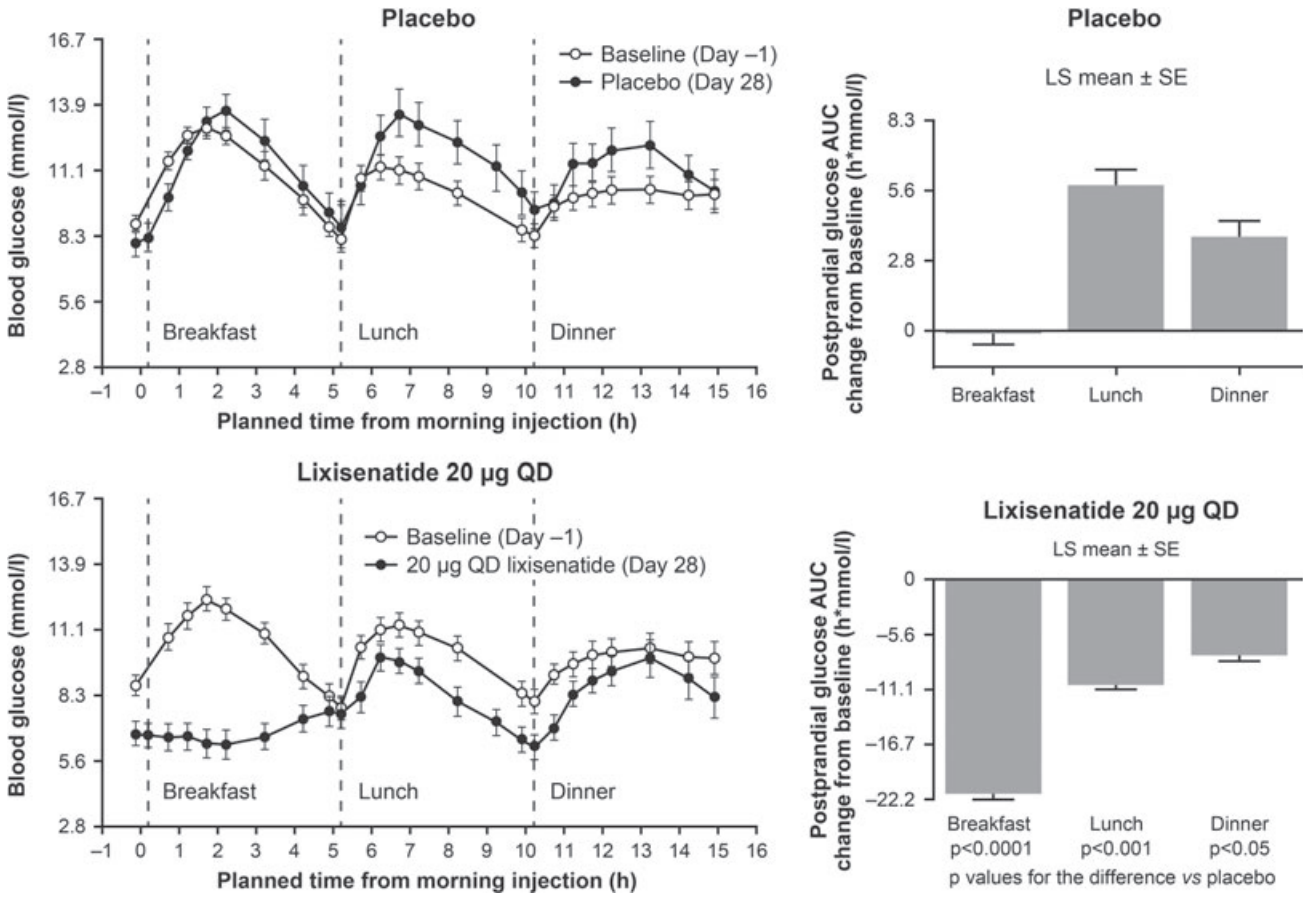

Figure 4. Change in postprandial plasma glucose (area under the curve) from baseline on day 28 after 4 weeks of treatment [53]. AUC, area under the curve; LS, least squares; QD, once daily; SE, standard error.

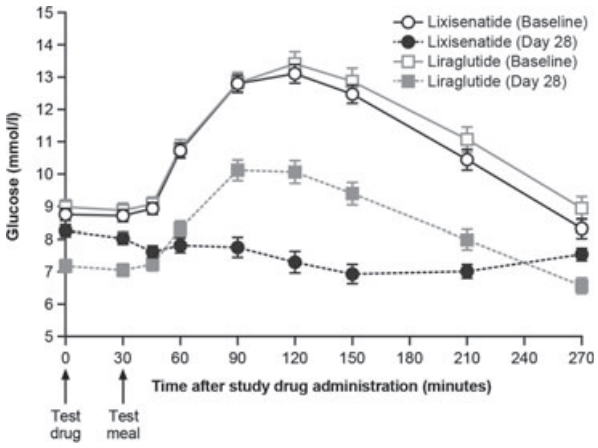

Figure 5. Mean postprandial plasma glucose profiles (glucose $AUC_{0:30-4:30h}$). Adapted with permission from Ref. [58] from John Wiley and Sons.

in a 4-week, randomized, open-label, repeated-dose, phase II study in people with T2DM insufficiently controlled on metformin ≥1.5 g/day [58]. The primary endpoint was change in PPG ($\Delta AUC_{0:30-4:30\,h}$) after 4 weeks, based on a standardized breakfast test meal. Results demonstrated that lixisenatide achieved a significantly greater reduction in PPG (glucose $AUC_{0:30-4:30\,h}$) compared with liraglutide ($p < 0.0001$; Figure 5). In addition, lixisenatide provided a significantly greater reduction in maximum PPG excursion compared with liraglutide (−3.9 mmol/l with lixisenatide vs. −1.4 mmol/l with liraglutide, $p < 0.0001$), with a greater proportion of lixisenatide-treated subjects (69%) achieving a 2-h PPG level <7.8 mmol/l at 28 days compared with liraglutide-treated subjects (29%). Lixisenatide achieved a statistically significant greater decrease in post-meal glucagon from baseline to week 4 ($p < 0.05$ vs. liraglutide). Postprandial insulin and C-peptide levels were significantly lower with lixisenatide versus liraglutide ($p < 0.0001$ for both). Decreases in pro-insulin were not significantly different between groups. The fact that insulin secretion was decreased with lixisenatide and relatively unchanged with liraglutide reflects the markedly lower PPG levels with lixisenatide [42,48,52], as a result of greater inhibition of gastric emptying with lixisenatide compared with liraglutide. Both lixisenatide and liraglutide decreased FPG, although the reduction was greater with liraglutide (−0.3 vs. −1.3 mmol/l, respectively; $p < 0.0001$). The mean HbA1c decreased in both treatment groups [from 7.2% (55 mmol/mol) to 6.9% (52 mmol/mol) with lixisenatide vs. 7.4% (57 mmol/mol) to 6.9% (52 mmol/mol) with liraglutide;

$p < 0.01$ for difference between groups], as did body weight (−1.6 vs. −2.4 kg, respectively; $p < 0.01$). Supine heart rate decreased by up to −3.6 beats per minute with lixisenatide in contrast to an increase of up to 5.3 beats per minute with liraglutide. Lixisenatide and liraglutide were both well tolerated, although the overall incidence of adverse events (AEs) was lower with lixisenatide (58%) compared with liraglutide (73%). Four subjects were discontinued due to AEs: two on lixisenatide (2.6%) due to allergic reactions (drug hypersensitivity and injection-site rash) and two on liraglutide (2.8%) due to GI events (severe diarrhoea/abdominal cramps/pain and moderate nausea/mild dyspepsia). There were no serious AEs and no cases of hypoglycaemia reported during the study [58].

Efficacy-to-Tolerability Ratio of Lixisenatide 20 μg Once Daily

To evaluate the dose–response relationship of lixisenatide, a 13-week, randomized, double-blind, placebo-controlled, parallel-group study was undertaken in which lixisenatide was administered at doses of 5, 10, 20 or 30 μg once or twice daily in 542 people with T2DM inadequately controlled on metformin [56]. The primary endpoint was change in HbA1c from baseline to week 13. Results demonstrated that all lixisenatide dosages significantly improved glycaemic control from a mildly elevated mean baseline HbA1c of 7.55% (59 mmol/mol), with reductions ranging from 0.47 to 0.87% (5.1–9.5 mmol/mol) among the different dosing regimens (Figure 6) versus 0.18% (2.0 mmol/mol) with placebo (all $p < 0.01$ vs. placebo) [56]. A dose–response relationship with HbA1c level was seen for both the once- and twice-daily regimens of lixisenatide, with improvements in HbA1c being observed as early as week 5. Target HbA1c < 7% (53 mmol/mol) at study end was achieved in 68% of those receiving lixisenatide 20 and 30 μg once-daily versus only 32% receiving placebo ($p < 0.0001$) [59]. In addition, dose-dependent improvements were observed for FPG, PPG and average self-monitored 7-point blood glucose levels. Weight changes ranged from −3.9 to 2.0 kg with lixisenatide versus −1.9 kg with placebo. The most frequent AEs were GI events, which were primarily dose-dependent nausea. The efficacy of lixisenatide appeared to reach a plateau at a dose of 20 μg once-daily, with further dosage increases offering limited additional glycaemic benefit relative to the tolerability profile. This study was of a relatively short duration (13 weeks). A dose-effect plateau has also been observed with liraglutide doses [59]. This pivotal regulatory study of lixisenatide concluded that the 20 μg dose administered once-daily provided the best efficacy-to-tolerability ratio. Accordingly, all the subsequent GetGoal, phase III trials for lixisenatide utilized a once-daily dosing regimen of 20 μg [59].

The Getgoal Lixisenatide Phase III Clinical Trial Programme

Table S1 provides an overview of data from the phase III trials (the GetGoal programme) to assess the efficacy and safety of lixisenatide for the treatment of adult subjects with T2DM. In these studies, lixisenatide was evaluated as monotherapy [48], as add-on therapy to metformin [49–51], sulphonylurea [52] or pioglitazone [60], and in combination with basal insulin [40–42].

Lixisenatide as Monotherapy

The first results to be reported were those of the GetGoal-Mono trial, which demonstrated that 12 weeks of lixisenatide 20 μg administered once-daily as monotherapy provided significant improvements in glycaemic control [48]. In this study, 361 subjects with T2DM [HbA1c 7–10% (53–86 mmol/mol)] were randomized to one of four once-daily treatment regimens: lixisenatide one-step dose increase (10 μg for 2 weeks and then 20 μg; n = 119), lixisenatide two-step dose increase (10 μg for 1 week, 15 μg for 1 week and then 20 μg; n = 120), placebo one-step (n = 61) or placebo two-step (n = 61) (placebo groups were combined for analysis) [48]. Both lixisenatide dose-increase groups were associated with statistically significant improvements in HbA1c compared with placebo [least

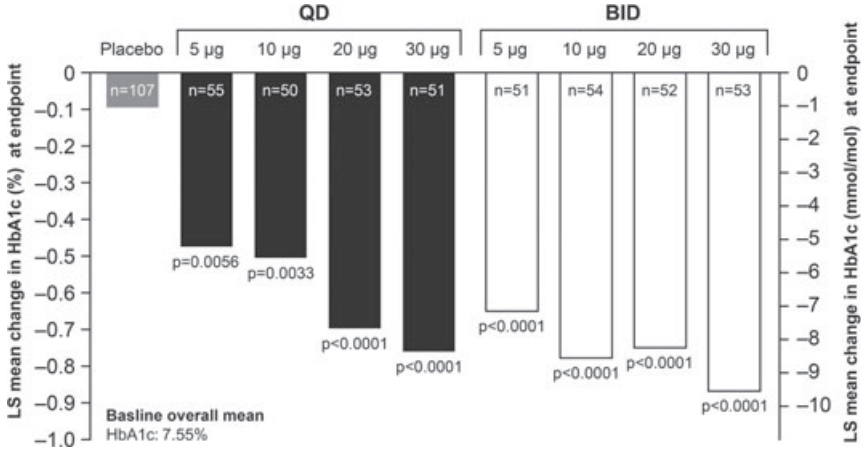

Figure 6. Least squares mean change in HbA1c following 13 weeks' treatment with lixisenatide once- or twice-daily, according to dosage and regimen. BID, twice-daily; HbA1c, glycated haemoglobin; LS, least squares; QD, once-daily. Adapted with permission from Ref. [56].

squares mean (LSM) change vs. placebo: −0.66 for one-step; −0.54% for two-steps ($p < 0.0001$; Table S2)]. In addition, significantly more subjects in the lixisenatide groups achieved HbA1c ≤ 6.5% (≤48 mmol/mol): 25.4% one-step, 31.9% two-steps, and HbA1c < 7% (<53 mmol/mol): 46.5% one-step, 52.2% two-steps, compared with placebo (12.5 and 26.8%, respectively). There was a pronounced effect of lixisenatide on PPG, with a significant and clinically meaningful improvement in both the 2-h PPG ($p < 0.0001$) excursions following the meals. A significant decrease in FPG was also observed in both lixisenatide groups versus placebo. Decreases in body weight of approximately 2 kg were observed in both lixisenatide- and placebo-treated groups. Overall, lixisenatide was well tolerated, with no difference in AEs between the one-step and two-step dose-increase regimens (Table S3). As expected, the most common AEs were GI events. Symptomatic hypoglycaemia occurred in 1.7% of lixisenatide-treated and 1.6% of placebo-treated subjects, with no severe episodes being reported (Table S3) [48].

Lixisenatide in Combination With Oral Antidiabetic Therapy

Five studies have evaluated lixisenatide as add-on therapy to oral antidiabetic agents (metformin, sulphonylurea and pioglitazone). These are summarized below.

T2DM Insufficiently Controlled on Metformin

Three studies (GetGoal-M [49], GetGoal-F1 [50] and GetGoal-X [51]) have examined the efficacy and safety of lixisenatide once-daily as add-on therapy to metformin in adults with T2DM. In GetGoal-M, 680 subjects inadequately controlled on metformin alone [HbA1c 7–10% (53–86 mmol/mol)] were randomized to one of four treatment arms: lixisenatide morning dose (before breakfast administration, AM) (n = 255), lixisenatide evening dose (before dinner administration, PM) (n = 255), placebo morning dose AM (n = 85) and placebo evening dose PM (n = 85) over a period of 24 weeks (placebo groups were combined for analysis) [49]. Both the morning and evening doses of lixisenatide significantly reduced HbA1c ($p < 0.0001$) and FPG ($p < 0.005$) versus placebo (Table S2; Figures 7 and 8). Lixisenatide also increased the proportion of subjects achieving HbA1c < 7.0% (53 mmol/mol) [49,50]. In addition, the lixisenatide morning dose regimen significantly decreased 2-h PPG glucose excursion versus the placebo morning dose regimen after a standardized breakfast meal test (morning injection arms only) (Table S2, Figures 7 and 8). Mean body weight decreased similarly in the lixisenatide and placebo groups. The percentage of subjects with AEs and serious AEs was comparable between the lixisenatide groups (69.4% AM/69.4% PM, and 2.0% AM/3.1% PM, respectively) and the combined placebo group (60.0 and 1.2%, respectively).

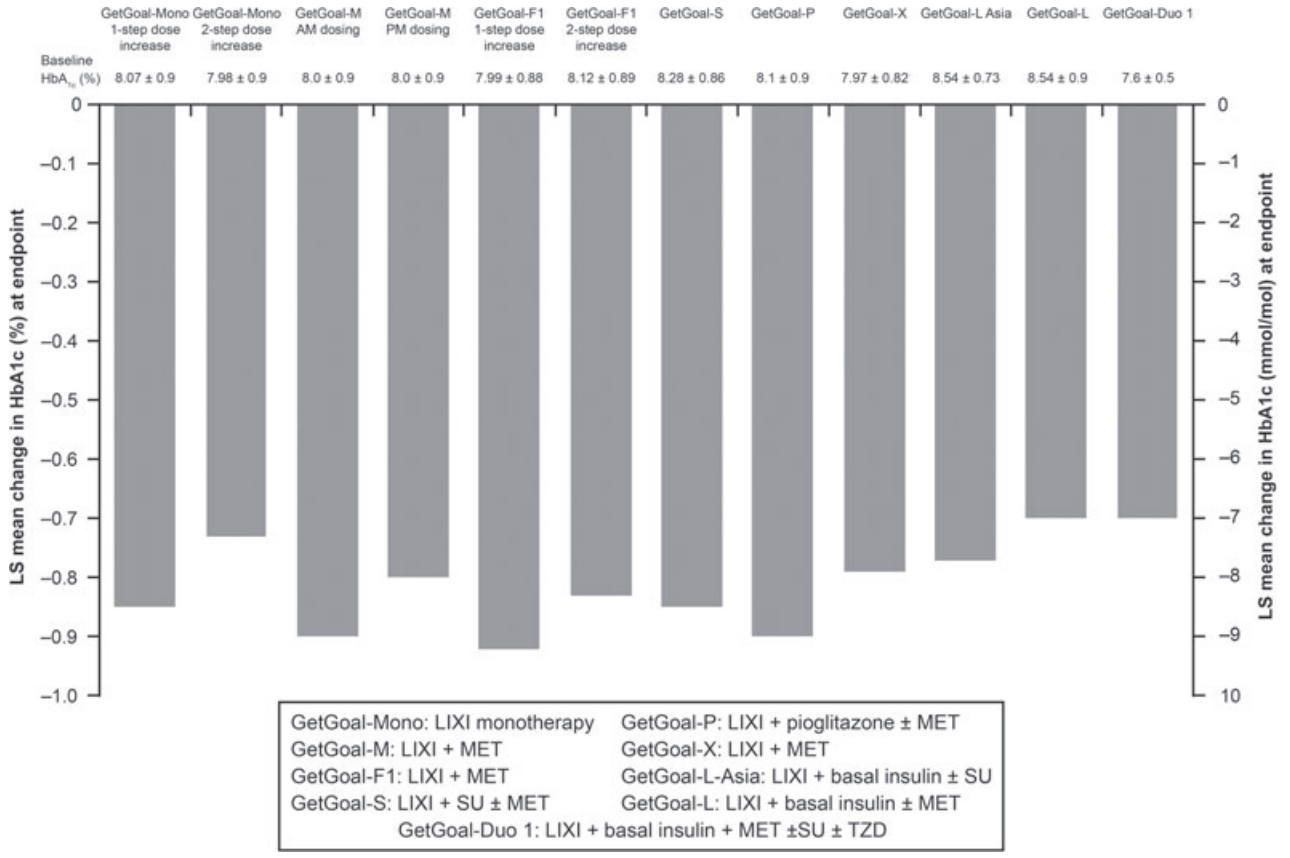

Figure 7. Mean change from baseline in HbA1c (%) at endpoint; results from the GetGoal Phase III Clinical Trial programme with lixisenatide [40–42, 48–52, 60]. HbA1c, glycated haemoglobin; LIXI, lixisenatide; LS, least squares; MET, metformin; SU, sulphonylurea; TZD, thiazolidinedione.

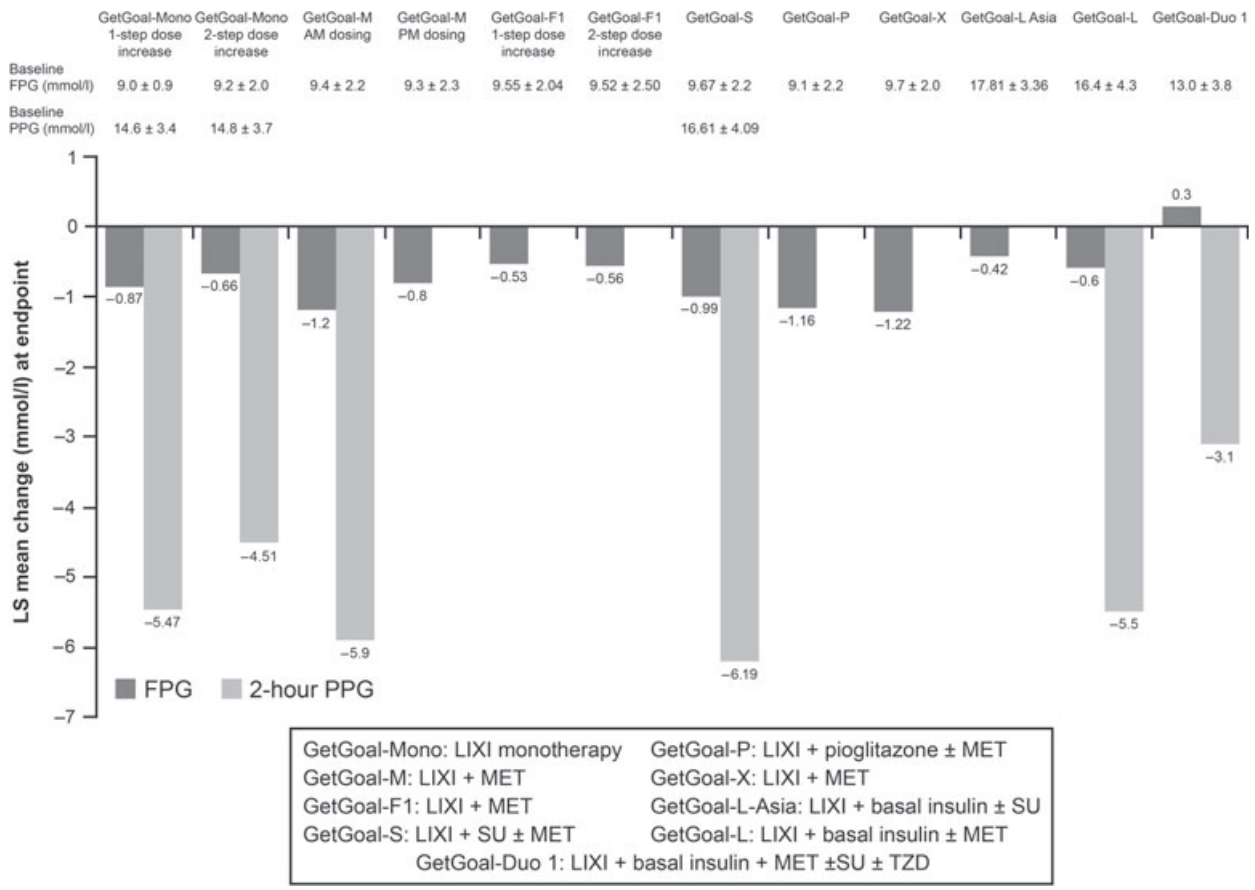

Figure 8. Mean change from baseline in FPG and PPG (mmol/l) at endpoint; results from the GetGoal Phase III Clinical Trial programme with lixisenatide [40–42, 48–52, 60]. FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; LIXI, lixisenatide; LS, least squares; MET, metformin; PPG, postprandial plasma glucose; SU, sulphonylurea; TZD, thiazolidinedione.

The incidence of symptomatic hypoglycaemia was low in both lixisenatide and placebo groups (2.4% AM, 5.1% PM vs. 0.6% for placebo) (Table S3) [49].

In GetGoal-F1, 482 people with T2DM inadequately controlled by metformin [HbA1c 7–10% (53–86 mmol/mol)] were randomized to one of four regimens: lixisenatide one-step dose increase (10 µg for 2 weeks then 20 µg; n = 161), lixisenatide two-step dose increase (10 µg for 1 week, 15 µg for 1 week, then 20 µg; n = 161), placebo one-step (n = 81) or placebo two-step (n = 79) for 24 weeks [50]. For the purpose of the analysis, the placebo groups were combined. At week 24, there were significant improvements in HbA1c in both lixisenatide groups versus placebo ($p < 0.0001$). Moreover, significantly more subjects in the lixisenatide groups achieved HbA1c ≤ 6.5% (≤48 mmol/mol) and <7.0% (<53 mmol/mol) versus placebo ($p < 0.001$). There were also significant improvements in FPG and body weight with lixisenatide versus placebo [50]. The incidence of subjects with AEs and serious AEs was comparable in the lixisenatide and placebo groups, with the most frequent being nausea and vomiting. Importantly, there was no significant difference in the percentage of subjects with symptomatic hypoglycaemia between the lixisenatide and placebo, and there were no cases of severe hypoglycaemia reported [50].

GetGoal-X was the first head-to-head trial with another GLP-1 RA, which was a randomized, open-label, 24-week trial that compared lixisenatide 20 µg once-daily with exenatide 10 µg twice-daily as add-on therapy in 639 adults with T2DM inadequately controlled on metformin monotherapy (≥1.5 g/day) [51]. The primary objective of this study was to demonstrate non-inferiority of lixisenatide once-daily to exenatide twice-daily in terms of HbA1c reduction at the end of the 24-week trial. Non-inferiority was proven if the upper limit of the two-sided 95% CI of the difference in adjusted mean HbA1c change from baseline to week 24 between lixisenatide and exenatide was ≤0.4%. The findings demonstrated that lixisenatide once-daily achieved the primary efficacy objective of non-inferiority to exenatide twice-daily in terms of HbA1c reduction from baseline to week 24. Improvements in mean FPG and the proportion of subjects achieving HbA1c <7.0% (53 mmol/mol) were comparable between treatment groups. Mean body weight decreased from baseline in both groups: −2.96 kg for lixisenatide once-daily and −3.98 kg for exenatide twice-daily with a mean difference of 1.02 (95% CI: 0.456, 1.581; Table S2) [51]. During the 24-week treatment period, the overall rates of AEs and serious AEs were similar in the lixisenatide once-daily and exenatide twice-daily groups (Table S3). The most common AEs in both groups were GI

in nature, mainly nausea. GI events were less frequent in the lixisenatide once-daily group, with significantly fewer subjects reporting nausea (24.5%) compared with the exenatide twice-daily group (35.1%). In addition, significantly fewer subjects experienced symptomatic hypoglycaemia in the lixisenatide once-daily group (2.5%) compared with the exenatide twice-daily group (7.9%) and no severe hypoglycaemia events were reported during the 24-week treatment period.

GetGoal-S was the largest trial in the clinical programme, involving 859 subjects insufficiently controlled on sulphonylurea, with or without metformin [HbA1c 7–10% (53–86 mmol/mol)]. Subjects were randomized to receive either lixisenatide 20 µg once-daily (n = 573) or placebo (n = 286) in a two-step dose-increase regimen [52]. At baseline, 16% of subjects were receiving sulphonylurea alone, with the remainder receiving a sulphonylurea in combination with metformin. Compared with placebo, lixisenatide significantly reduced HbA1c, increased the proportion of subjects achieving HbA1c < 7.0% (<53 mmol/mol) and significantly lowered 2-h PPG, FPG and body weight ($p < 0.0001$ for all efficacy measures) [52]. The overall incidence of subjects with AEs was 68.3% in the lixisenatide group and 61.1% in the placebo group; the difference between groups was mainly attributable to GI events (Table S3). Lixisenatide did not significantly increase symptomatic hypoglycaemia, although one case of severe hypoglycaemia was reported in the lixisenatide group (0.2%) [52].

In the GetGoal-P trial, 484 subjects with T2DM insufficiently controlled by pioglitazone 30 mg/day, with or without metformin, were randomized to receive lixisenatide 20 µg once daily or placebo [60]. Results demonstrated that lixisenatide produced significantly greater reductions in HbA1c than placebo ($p < 0.0001$), with a greater proportion of lixisenatide-treated subjects achieving HbA1c < 7.0% (<53 mmol/mol) compared with placebo-treated subjects ($p < 0.0001$) [60]. FPG was also significantly reduced with lixisenatide versus placebo ($p < 0.0001$). There was only slight weight loss observed with lixisenatide and slight weight gain with placebo (difference not significant). Overall, lixisenatide was well tolerated, with a similar proportion of AEs and serious AEs being observed in the two treatment groups (Table S3). Symptomatic hypoglycaemia rates were low in both treatment groups and there were no cases of severe hypoglycaemia in either group [60].

Lixisenatide in Combination With Basal Insulin With or Without Oral Antidiabetic Therapy

Three randomized, double-blind, placebo-controlled, 24-week studies have specifically examined whether the marked postprandial effects observed with lixisenatide could complement the fasting glucose reduction provided by basal insulin therapy in the largest number of basal insulin-treated persons with T2DM to date [40–42]. GetGoal-L-Asia was the first study that reported evaluated lixisenatide in combination with basal insulin [42]. In this trial, 311 Asian participants with T2DM not achieving glycaemic control with basal insulin [glargine, detemir, NPH (neutral protamine hagedorn)], with or without a sulphonylurea, were randomized to add either lixisenatide 20 µg once-daily (n = 154) or placebo (n = 157) in addition to their existing treatment regimen. The results demonstrated that the addition of lixisenatide to basal insulin significantly improved glycaemic control; lixisenatide significantly improved HbA1c versus placebo (LS mean difference vs. placebo: −0.88%; $p < 0.0001$) and allowed more subjects to achieve a HbA1c < 7% (<53 mmol/mol, 35.6 vs. 5.2%, respectively) and ≤6.5% (≤48 mmol/mol, 17.8 vs. 1.3%, respectively) (Table S2, Figures 7 and 8). Lixisenatide also significantly improved 2-h PPG, glucose excursion, average 7-point self-monitored blood glucose and FPG levels. However, there was no significant difference in body weight reduction between the groups. Overall, lixisenatide was well tolerated and, as expected for the GLP-1 class of drugs, the most frequent AEs were GI in nature, mainly nausea and vomiting. In total, 61.0% in the lixisenatide group and 14.6% in the placebo group reported a GI AE, although these events were mostly transient, occurring during the initial weeks of treatment, with only few patients discontinuing treatment due to nausea or vomiting (only 3.9 and 2.6% for lixisenatide and placebo, respectively). Symptomatic hypoglycaemia was more frequent with lixisenatide (42.9%) versus placebo (23.6%), a finding that was frequently observed in people treated with a combination of insulin and sulphonylureas. However, in the subgroup of those not receiving a sulphonylurea, the incidence of hypoglycaemia in those treated with lixisenatide was similar to that of placebo: 32.6 versus 28.3%, respectively [42].

The second trial to investigate the benefits of lixisenatide in combination with basal insulin was GetGoal-L. In this trial, lixisenatide was added to basal insulin [glargine (50%), NPH (40%) and detemir (9%)] in 496 subjects with T2DM inadequately controlled on basal insulin ± metformin. In subjects with baseline HbA1c ≤7.5% (<58 mmol/mol) at screening, the basal insulin dose was initially reduced by 20% at randomization and thereafter progressively increased between weeks 4 and 12 to the dosage used at screening visit. After week 12, no further titrations were allowed except for reductions in response to hypoglycaemia. Subjects were randomized to add-on lixisenatide 20 µg once-daily or placebo for 24 weeks [40]. Compared with placebo, lixisenatide significantly reduced HbA1c, 2-h PPG after a standardized breakfast and body weight (Table S2, Figures 7 and 8). In addition, more subjects receiving lixisenatide achieved HbA1c <7% (<53 mmol/mol) than with placebo ($p < 0.0001$). At endpoint, the insulin dose was reduced more with lixisenatide than with placebo ($p = 0.012$). The majority of AEs were GI in nature (Table S3). A comparable proportion of subjects treated with lixisenatide and placebo reported symptomatic hypoglycaemia (27.7 vs. 21.6%); four cases of severe hypoglycaemia occurred in the lixisenatide group (Table S3) [40].

The third trial, GetGoal-Duo-1, investigated lixisenatide 20 µg once-daily as add-on therapy to titrated glargine in subjects with T2DM inadequately controlled on metformin, with or without a sulphonylurea, and/or with or without a thiazolidinedione [41,42]. Basal insulin glargine was initiated and titrated in a 12-week run-in phase to achieve a FPG of 4.4–5.6 mmol/l. Subjects with HbA1c ≥ 7.0% (≥53 mmol/mol) and ≤9.0% (≤75 mmol/mol), and whose mean FPG was ≤7.8 mmol/l, were then randomized to a

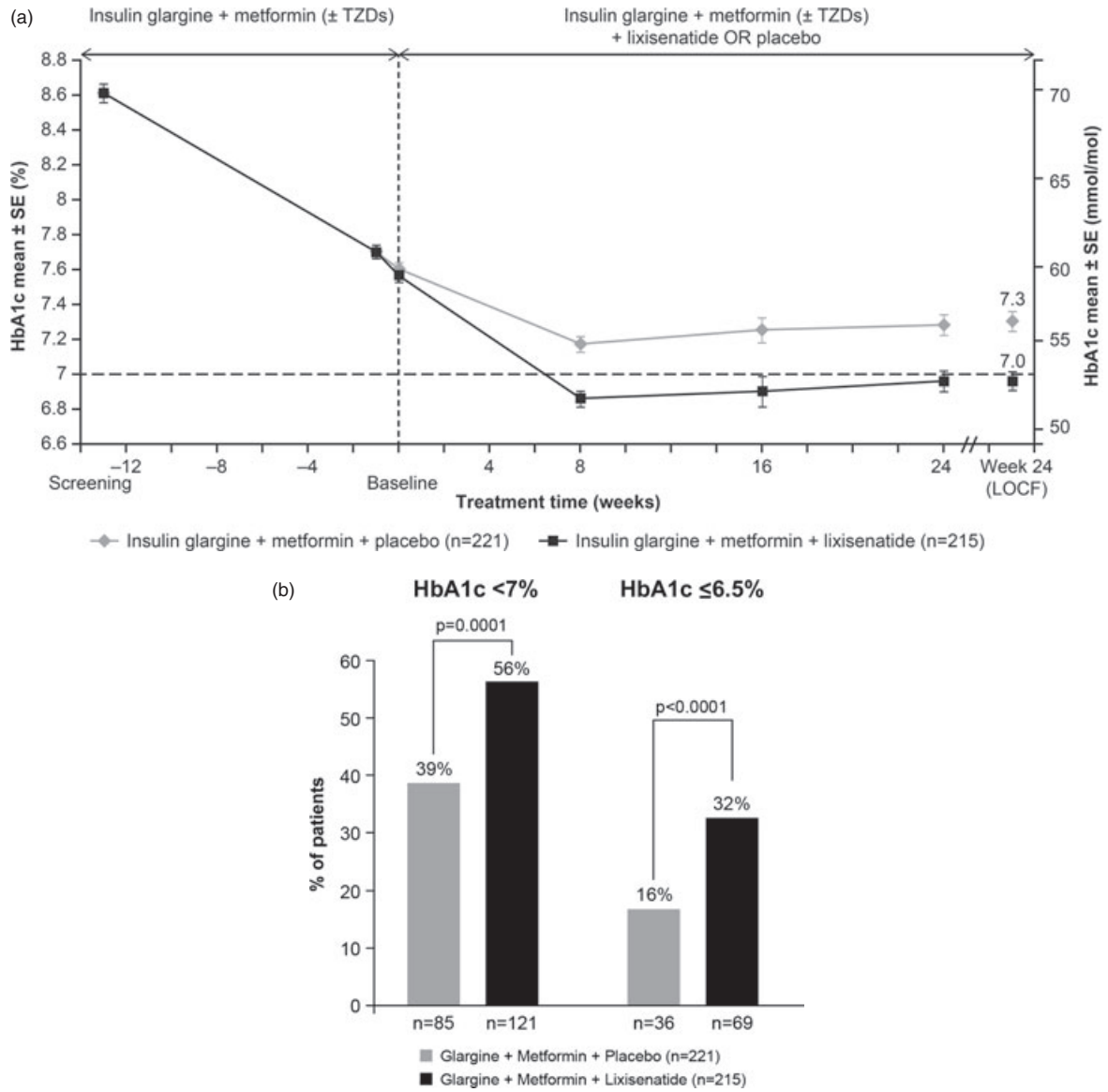

Figure 9. (A) Reduction in HbA1c over time and (B) proportion of subjects achieving HbA1c < 7% (<53 mmol/mol) and ≤6.5% (≤48 mmol/mol) for lixisenatide and placebo as add-on to glargine in the GetGoal-Duo-1 study [41]. HbA1c, glycated haemoglobin; LOCF, last observation carried forward; SE, standard error; TZD, thiazolidinedione.

morning dose of lixisenatide (n = 223) or placebo (n = 223) for 24 weeks, allowing glargine dose titration to be continued. During the screening phase, sulphonylureas were halted; all patients were receiving metformin and 12% were also receiving a thiazolidinedione. HbA1c decreased during the run-in phase from 8.6% (70 mmol/mol) to 7.6% (60 mmol/mol) (Figure 9A). Lixisenatide further reduced HbA1c versus placebo at endpoint (LS mean difference: −0.32%; $p < 0.0001$). Moreover, a greater proportion of lixisenatide-treated subjects achieved HbA1c < 7.0% (<53 mmol/mol) compared with those on placebo (Table S2; Figure 9B). Lixisenatide also significantly improved the 2-h PPG (after a standardized breakfast) and had a beneficial lowering effect on body weight despite glargine titration (Table S2). Overall, lixisenatide was well tolerated, with the most common GI events being nausea and vomiting (Table S3). Symptomatic hypoglycaemia was more frequent with lixisenatide (22.4%) versus placebo (13.5%) [41].

Comparison of Lixisenatide in Adults Aged 65 years and Over and 75 years and Over

A subanalysis of six randomized, placebo-controlled studies from the GetGoal Phase III programme assessed the efficacy (HbA1c) and safety (overall AEs, GI events and hypoglycaemia) of lixisenatide 20 µg once-daily in 379 subjects ≥65 years old, including 48 subjects ≥75 years old, during the main 12-week GetGoal-Mono [48] or the 24-week studies (GetGoal-M, -F1, -S, -L, -L-Asia) [61]. Results demonstrated that the efficacy profiles were similar regardless of age, with comparable decreases in HbA1c for those ≥65 years old and for those

≥75 years old, with significantly greater decreases versus placebo in both age categories. Likewise, the incidences of AEs, GI AEs and symptomatic hypoglycaemia were also comparable, regardless of age [61].

Discussion

Effective treatment of most subjects with T2DM eventually requires a multidisciplinary approach, including both lifestyle and pharmacological interventions [1]. Individualization of care is now well accepted as being central to management of hyperglycaemia in T2DM, with treatment being tailored to the individual's preferences, needs and values, taking into consideration factors such as glycaemic control, lifestyle, body weight, duration of disease, and the constraints imposed by age and co-morbidity [1].

Over the past decade, one of the most important developments in the management of T2DM relates to the incretin hormone GLP-1, a gut-derived hormone that is secreted in response to nutrients, which has metabolic and other important physiological effects [9–16]. One therapeutic strategy developed to take advantage of these actions is the use of GLP-1 RAs, which have a more extended half-life than native GLP-1 due to reduced degradation by the enzyme DPP-4. The development of the first two GLP-1 RAs, exenatide and liraglutide, represented a significant advancement in the treatment of T2DM [62]. Both of these agents have been shown to improve glycaemic control, while reducing or eliminating the risk of hypoglycaemia and preventing weight gain [30, 44]. The diverse actions of this class make GLP-1 RAs an appealing addition to the current therapeutic options for treating T2DM. They are particularly beneficial for certain populations of T2DM – such as obese individuals, for whom weight gain poses a significant clinical risk, and especially in those at risk of hypoglycaemia with co-morbidities such as cardiovascular diseases.

Lixisenatide is a once-daily GLP-1 RA for the treatment of T2DM. The efficacy and safety of lixisenatide 20 µg once-daily in adults with T2DM has been extensively evaluated in the GetGoal Phase III Clinical Trial programme. The first published results demonstrate that lixisenatide exhibits the properties expected of a GLP-1 RA in terms of improving overall glycaemic control (as assessed by HbA1c), with significant improvements being reported in 2-h PPG, blood glucose excursions and FPG levels in subjects receiving lixisenatide monotherapy [48] or lixisenatide as add-on therapy to metformin [49–51], sulphonylurea [52] or pioglitazone [60]. Importantly, the pronounced effect of lixisenatide on PPG provides a clear rationale for combining it with basal insulins [40–42]. The efficacy of lixisenatide has been attributed to its ability to significantly retard gastric emptying and restore or improve first- and second-phase insulin release in response to an intravenous glucose challenge [53–55]. The inhibitory effect of lixisenatide on gastric emptying is the predominant contributing factor for lowering PPG [53]. This effect is less evident with GLP-1 RAs possessing a more prolonged duration of action. Indeed, it appears that short-acting (prandial) GLP-1 RAs primarily lower PPG levels through inhibition of gastric emptying, as well as their action on β-cell and α-cell function, whereas the longer-acting preparations exert their effect primarily on FPG, via their predominant effect on β-cell function [8]. Delayed gastric emptying could potentially be associated with an increase in GI side-effects. However, studies have indicated that GI symptoms do not correlate with the rate of gastric emptying in T2DM [63]. This is supported by the fact that GI side-effects with GLP-1 RAs are generally transient and subside within a few weeks without the need for specific treatment [64]. The improvements in glycaemic control for lixisenatide were accompanied by a low risk of hypoglycaemia and a beneficial effect on weight. AEs were similar to those observed for other GLP-1 RAs, with the most frequent being transient GI effects such as nausea and vomiting. Although GI events were more frequent for lixisenatide than placebo, these events generally occurred during the first weeks of treatment, resolved with time, and the need for discontinuation of treatment was relatively infrequent across the studies. Notably, results from a head-to-head trial that demonstrated non-inferiority for HbA1c reduction with once-daily lixisenatide compared with twice-daily exenatide, also suggested less hypoglycaemia and a more favourable GI tolerability profile with lixisenatide [51]. Longer-term studies are required to further assess the efficacy and safety of GLP-1 RAs, such as lixisenatide.

Intensifying insulin treatment to improve glycaemic control is frequently associated with an increased risk of hypoglycaemia and weight gain [62]. As GLP-1 RAs are associated with a low incidence of hypoglycaemia and weight loss, the combination of long-acting basal insulin and a GLP-1 RA has become an attractive proposition. Potential complementary effects and treatment benefits of the combination of basal insulin and GLP-1 RAs are summarized in Table 1. Results from a recent parallel, randomized, placebo-controlled trial reported that adding twice-daily exenatide injections improved glycaemic control without increased hypoglycaemia or weight gain in those with uncontrolled T2DM who were receiving insulin glargine treatment [44]. As part of the lixisenatide GetGoal Phase III Clinical Trial programme, three studies were undertaken to evaluate lixisenatide in combination with basal insulin in subjects on a stable insulin dose or who were insulin naive. Importantly, GetGoal-L and GetGoal-L-Asia have evaluated the effects of adding lixisenatide in those not achieving adequate

Table 1. Differential physiological effects of basal insulin and GLP-1 receptor agonists.

Basal insulin	GLP-1 receptor agonists
Main effect on FPG, some effects on PPG	Effect on PPG (particularly short-acting GLP-1 RAs) Effect on FPG (particularly long-acting GLP-1 RAs)
Induces 'rest' of pancreatic β-cell function	Glucose-dependent insulin release
Body weight increase	Weight reduction
Increased risk of hypoglycaemia	Limited risk of hypoglycaemia

FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; PPG, postprandial plasma glucose.

control on established basal insulin [40,42], whereas GetGoal-Duo-1 has assessed the combination of optimized insulin glargine therapy and lixisenatide in those who had very recently started insulin therapy and achieved near-normal FPG values [41]. Results demonstrated that lixisenatide as add-on therapy to basal insulin significantly improved glycaemic control, with a pronounced reduction in PPG with either no weight gain or weight loss. Overall, lixisenatide was well tolerated in these three studies, with the most frequent AEs being GI in nature [40–42]. The combination of lixisenatide and basal insulin may prove to be particularly beneficial in certain T2DM populations, such as those who are unable to reach target HbA1c levels despite achieving relatively acceptable FPG control, the elderly, or those with co-existing obesity for whom weight gain is of primary concern. GLP-1 RAs would therefore be an alternative to rapid-acting insulin at meal-times after titration of basal insulin to achieve near-normal FPG but where HbA1c remains above 7.0% (53 mmol/mol).

Although the results from the GetGoal Phase III Clinical Trial programme are promising, a number of these studies still await to be published. In addition, lixisenatide has not yet been compared with liraglutide in a long-term trial. A factor that may distinguish lixisenatide from liraglutide is its strong PPG effect, which contrasts to the main FPG efficacy of liraglutide. As demonstrated in a 28-day, randomized, open-label, phase II study, lixisenatide 20 μg had a significantly greater PPG-lowering effect than liraglutide (1.8 mg once-daily) during a test meal (breakfast), which was accompanied by a significant decrease in glucagon levels [56]. A reduction in insulin and C-peptide levels were also seen, probably due to the marked effect of lixisenatide on gastric emptying. The long-term clinical relevance of the differential effect on PPG versus FPG remains to be established. However, lixisenatide can provide additional support for those subjects in whom a therapeutic response is difficult to achieve with current antidiabetic therapies, especially in combination with basal insulin, to further improve glycaemic control and minimize weight gain.

Conclusions

Lixisenatide is a once-daily, GLP-1 RA for the treatment of T2DM. Clinical efficacy and safety have been demonstrated with monotherapy and as add-on therapy to metformin, sulphonylurea or pioglitazone. In addition, lixisenatide in combination with basal insulin has been shown to significantly improve glycaemic control, with a limited risk of hypoglycaemia and a beneficial effect on body weight – either weight loss or no weight gain. Lixisenatide, therefore, provides a relatively easy, once-daily, single-dose, add-on treatment in the management of T2DM, which typically requires a multi-drug approach. The advent of lixisenatide to the therapeutic armamentarium will enrich the category of GLP-1 RAs. Although additional studies will be conducted in the near future to better understand the full potential of this GLP-1 mimetic, lixisenatide already demonstrates unique and positive characteristics that differentiate it from other GLP-1 RAs. Primarily, unlike exenatide, lixisenatide is administered as a convenient once-daily dose and, unlike liraglutide, has a greater PPG-lowering effect. These properties of lixisenatide are relevant to its clinical use in the treatment of T2DM. Lixisenatide can be particularly valuable as add-on treatment to basal insulin when uncontrolled PPG prevents the goal of HbA1c < 7.0% (<53 mmol/mol), being reached despite achieving target FPG with the basal insulin. Further studies are needed to further establish the full potential of lixisenatide to address the different pathophysiological defects in T2DM and to optimize its use in combination with other antidiabetic agents, including insulin.

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Conflict of Interest

G. B. B. has received honoraria for consultation from Sanofi, Novartis and Eli Lilly. D. R. O. has received honoraria from Boehringer Ingelheim, Eli Lilly, Sanofi, Roche Diagnostics and Novo Nordisk for lectures and participation in advisory boards.

G. B. B. and D. R. O. conceptualized the structure of the article, participated in the analysis of the data and critically reviewed every draft of the manuscript.

Supporting Information

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

Table S1. Overview of the GetGoal Phase III Clinical Trial programme with lixisenatide [40–42, 48–52, 60].

Table S2. Overview of the efficacy results from the GetGoal Phase III Clinical Trial programme with lixisenatide [41–43, 49–53, 61].

Table S3. Overview of the safety results from the GetGoal Phase III Clinical Trial programme with lixisenatide [41–43, 49–53, 61].

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