CLINICAL INVESTIGATION

Design, findings and implications of the liraglutide Phase III clinical trial program

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Liraglutide is an analog of the human peptide hormone GLP-1 and a member of the GLP-1 receptor agonists class, which has recently been developed for treatment of Type 2 diabetes (T2D). Incretin-based therapies are an important step forward in the management of T2D as they can provide effective glycemic control without the hypoglycemia and weight gain associated with previous therapies. An extensive program of Phase III clinical trials was developed to test the efficacy and safety of liraglutide across the continuum of care in T2D. These trials have proven liraglutide to be well tolerated and effective in managing glycemia in a variety of treatment combinations and across a wide patient population. The Phase III trial program also demonstrated that liraglutide can provide the additional benefits of weight loss, reduction in systolic blood pressure, improvement in measures of β-cell function and increased treatment satisfaction.

Keywords: GLP-1 receptor agonist • glycemic control • HbA_{1c} • LEAD trials • liraglutide • Type 2 diabetes

Type 2 diabetes (T2D) is characterized by chronic hyperglycemia that is the result of impaired insulin sensitivity and secretion. Control of glycemia is the primary aim of treatment of T2D, as improvements are known to reduce the risk of the microvascular and macrovascular complications associated with the disease [1]. The level of glycosylated hemoglobin (HbA_{1c}) is commonly used as a measure of plasma glucose concentration over time and the importance of glycemic control in T2D is reflected in the HbA_{1c} goals that are set by internationally recognized bodies [2,3].

Although many therapies are available for control of hyperglycemia in T2D, they often cause weight gain or hypoglycemia, which can limit their effectiveness [2]. In recent years, however, increased understanding of the incretin hormones and their receptors has led to the development of two classes of incretin-based therapies: GLP-1 receptor agonists (RAs) and dipeptidyl peptidase-4 (DPP-4) inhibitors. These therapies represent an important step forward, as they can improve glycemic control with a low risk of hypoglycemia and without weight gain (and with weight loss in the case of GLP-1 RAs) [4].

This review specifically addresses the Phase III clinical trials of the GLP-1 RA liraglutide. Liraglutide is a recently developed analog of the human incretin hormone GLP-1 that is representative of the GLP-1 RA class and which has been tested in a wide patient population. Efficacy and tolerability findings from the trials will be discussed, as well as some of the implications for use of liraglutide in clinical practice.

Incretin-based therapies in T2D

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The term 'incretin effect' refers to the fact that a given amount of glucose results in greater secretion of insulin when administered orally than when administered intravenously. The effect is mediated by intestinal peptides that are secreted in response to food intake and is thought to contribute up to 70% of normal post-prandial insulin response [5]. The two most important incretin peptides are glucose-dependent insulinotropic polypeptide and GLP-1. In T2D, the incretin effect is impaired [6,7] and the discovery that exogenous infusion of GLP-1 can restore insulin secretion made GLP-1 an attractive therapeutic target [8–10]. As well as stimulating insulin production in a glucose-dependent manner, administration of GLP-1 was also found to suppress glucagon secretion in a glucose-dependent manner and slow gastric emptying. Additionally, positive effects on β-cell function were observed both *in vitro* and in animal models [5,11]. These effects are all highly desirable in the treatment of T2D, but the 2 min half-life of GLP-1 [12] means that the peptide itself is not therapeutically useful unless administered continuously.

The two classes of incretin-based therapies were developed to overcome the therapeutic limitations of GLP-1 and represent two different mechanisms to increase activation of the GLP-1 receptor. The DPP-4 inhibitors inactivate DPP-4, an enzyme that plays an important role in GLP-1 degradation, and can increase the concentration of native GLP-1 up to physiological levels [4]. By contrast, the GLP-1 RAs are exogenously administered peptides with resistance to DPP-4 that activate the GLP-1 receptor. GLP-1 RAs are administered at levels six- to ten-times that of native GLP-1 and so can provide supraphysiological levels of GLP-1 receptor activation [4].

Two GLP-1 RAs are currently available for use: liraglutide and exenatide. Liraglutide is an analog of human GLP-1, with 97% amino acid identity to the native peptide [4]. By contrast, exenatide is derived from exendin-4, a peptide found in the saliva of *Heloderma suspectum*, and has 53% amino acid identity with human GLP-1. As peptides, both liraglutide and exenatide are injected subcutaneously. Liraglutide has a half-life of 11–15 h and is administered once daily, while exenatide has a half-life of 2–4 h and must be administered twice daily [13,14,101,102]. Both GLP-1 RAs have been shown to provide glycemic control, as well as weight loss, reductions in systolic blood pressure (SBP) and improvement in measures of β-cell function [4].

Liraglutide

Liraglutide was developed from a series of GLP-1 analogs to which fatty acid moieties had been appended [15]. The molecule differs from native GLP-1 only in addition of a C-16 palmitate moiety to lysine 26 via a glutamate spacer and substitution of lysine for arginine at position 34. Liraglutide binds plasma albumin and self-associates into heptamers, both of which are thought to prolong the molecule's half-life [16,17]. Animal studies have provided proof-of-principle that liraglutide can improve glycemic control, reduce body weight and improve cardiovascular and β-cell function [18]. A series of successful early clinical trials subsequently determined that liraglutide can provide improvements in glycemic control and β-cell function in humans, paving the way for development of the Phase III trial program [19].

Liraglutide Phase III trial program: overview & design

The Phase III trial program was designed to assess the effects of liraglutide across the spectrum of disease progression in T2D. Liraglutide was studied as monotherapy and as an addition to oral antidiabetic drugs (OADs) used at different disease stages (Figure 1).

The six LEAD trials formed the core of the trial program. The LEAD-1–5 trials compared liraglutide to OADs and insulin glargine, and the LEAD-6 study was a head-to-head comparison of liraglutide and exenatide [20–25]. An additional trial, known as the 1860 study, provided a direct comparison of liraglutide to the DPP-4 inhibitor sitagliptin [26]. Overall, the Phase III trial program included more than 5000 adults, with over 3000 treated with liraglutide, and is a comprehensive study of liraglutide across the continuum of diabetes treatment.

The trials tested liraglutide in a range of treatment combinations. The LEAD-3 trial tested liraglutide as monotherapy [22]. LEAD-1 and -2 tested use as second-line therapy in combination with sulfonylurea (SU) or metformin [20,21]. LEAD-4 and -5 tested use as third-line therapy with metformin and SU/thiazolidinedione (TZD) [23,24]. In LEAD-6, patients used liraglutide with metformin and/or SU, and in the 1860 study, liraglutide was used in addition to metformin [25,26].

A similar design was used across the trials. In each trial, the primary efficacy end point was change in HbA_{1c} and secondary end points included change in fasting plasma glucose (FPG), body weight and SBP, as well as measures of β-cell function. Each trial had one or more liraglutide arms, as well as placebo and/or comparator arms [20–26]. Core study periods lasted 26 weeks, except in the case of LEAD-3, which lasted 52 weeks. Additionally, LEAD-2, -3 -6 and 1860 had extension periods; data from the LEAD-6, -3 and 1860 extensions are discussed here; the LEAD-2 extension is yet to be fully reported [27–29].

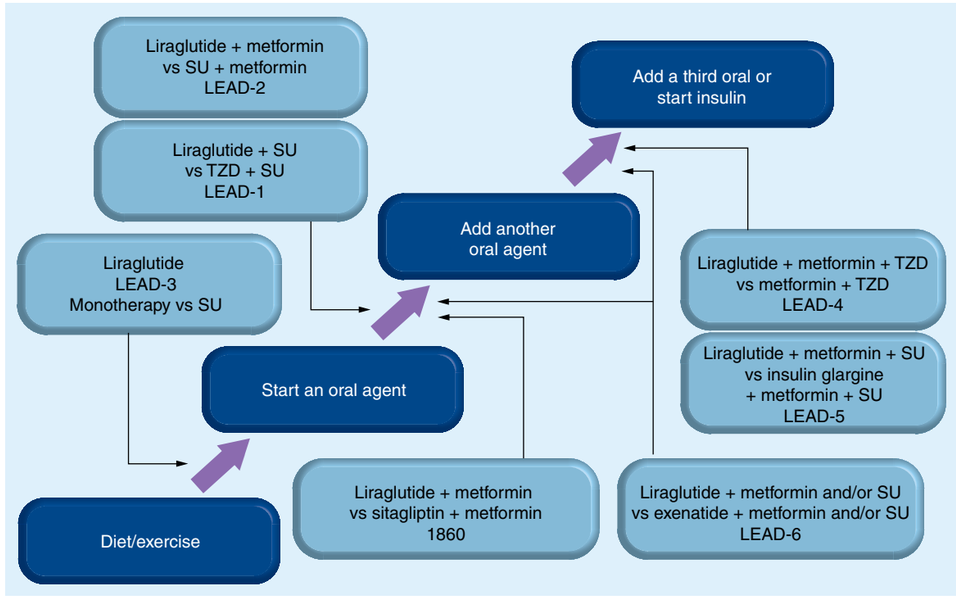

Figure 1. Overall design of the liraglutide Phase III trial program.
SU: Sulfonylurea; TZD: Thiazolidinedione.
Data taken from [20–26].

In all studies, liraglutide was injected subcutaneously, independent of meal times. Patients and investigators were blinded with respect to liraglutide or placebo in the LEAD-1–5 trials [20–24]. Liraglutide was available in one concentration and, to maintain blinding, patients receiving liraglutide placebo were randomized to injection volumes corresponding to the liraglutide doses tested. The LEAD-6 and 1860 trials, as well as the LEAD-3 trial extension were open label [25,26,29]. If patients were randomized to the active drug, they began treatment with liraglutide 0.6 mg daily for 1 eek, escalated to 1.2 mg for the next week and then to 1.8 mg daily thereafter if they were randomized to the 1.2- or 1.8-mg doses. All seven trials included the 1.8-mg dose, LEAD-1–4 and 1860 also included 1.2 mg, and LEAD-1 and -2 included 0.6 mg. This review focuses only on data from the two highest doses, as liraglutide 0.6 mg is now recommended only as a starting dose [101].

It should be noted that all liraglutide treatment combinations and doses trialed and discussed here may not be approved or recommended in all regions. In particular, liraglutide is not approved as monotherapy in mainland Europe or the UK [101,103]. Local guidelines should always be consulted before prescribing liraglutide.

Efficacy of liraglutide

Change in HbA_{1c}

Reductions in HbA_{1c} from baseline with liraglutide in the core periods of the Phase III trials ranged from 0.8–1.5% (Supplementary Table 1) [20–26]. Improvements were significantly greater with liraglutide than with comparators (TZD, SU, placebo, insulin glargine, exenatide and sitagliptin), except in LEAD-2, where addition of liraglutide to metformin treatment was comparable to addition of the SU glimepiride to metformin (Figure 2) [20–24].

However, improvements with liraglutide (0.8 and 1.1% with 1.2 and 1.8 mg, respectively) were significantly greater than with glimepiride (0.5%; $p = 0.0014$ and $p < 0.0001$ for liraglutide 1.2 and 1.8 mg, respectively) when both treatments were used as monotherapy for 52 weeks [22]. Reductions in HbA_{1c} with liraglutide were greater in patients who had previously been treated with only diet and exercise (1.2 and 1.6% for liraglutide 1.2 and 1.8 mg, respectively) than in patients who had substituted liraglutide for an OAD (0.5 and 0.7% for liraglutide 1.2 and 1.8 mg, respectively). The advantages of liraglutide on glycemic control were still evident after 2 years in patients who completed the LEAD-3 extension: overall HbA_{1c} reductions were 0.6% with glimepiride, compared with 0.9% with liraglutide 1.2 mg ($p = 0.0376$) and

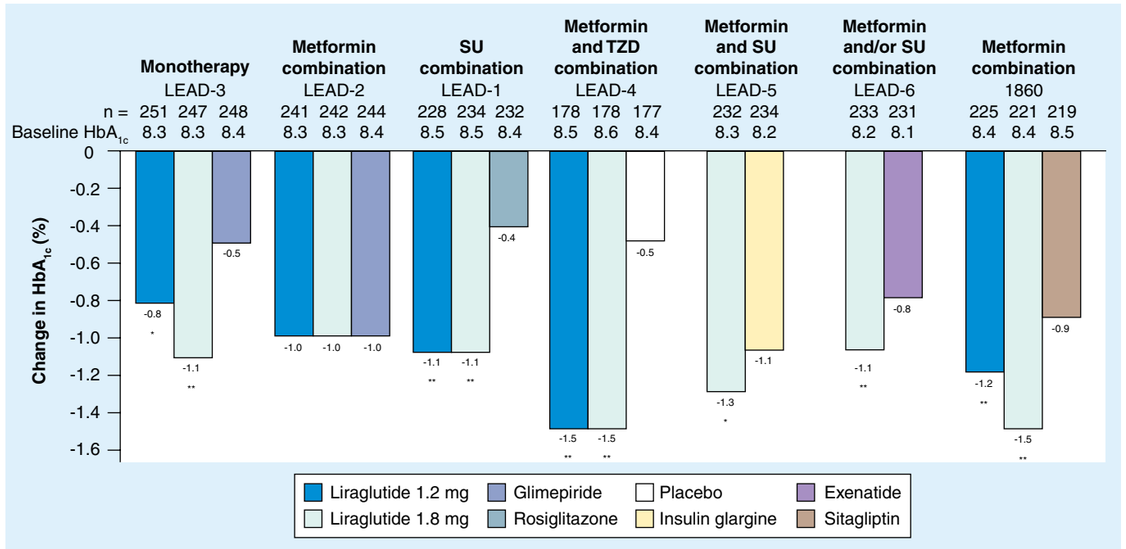

Figure 2. Change in glycosylated hemoglobin from baseline in the liraglutide Phase III studies.
*p < 0.005; **p < 0.0001 versus comparator.
SU: Sulfonylurea; TZD: Thiazolidinedione.
Data taken from [20–26].

1.1% with liraglutide 1.8 mg (p = 0.0016) [29].

In Europe, liraglutide is approved as dual and triple therapy with OADs [103], and the most pertinent data for healthcare practitioners in this area are from trials of liraglutide in combination with OADs. Liraglutide was used as dual therapy in LEAD-1 and -2, in combination with glimepiride or metformin, respectively [20,21]. Patients treated with liraglutide plus glimepiride in LEAD-1 had significantly greater reductions in HbA_{1c} (1.1% with both liraglutide 1.2 and 1.8 mg) than patients treated with rosiglitazone and glimepiride (0.4%; p < 0.0001 for both doses) [20]. Patients in LEAD-2 who were treated with liraglutide plus metformin had similar decreases in HbA_{1c} to those treated with glimepiride plus metformin (-1% in all groups) [21]. Importantly, patients taking liraglutide had greater weight loss and less frequent hypoglycemia than patients taking glimepiride. Additionally, patients previously on OAD monotherapy had greater HbA_{1c} improvements than those who substituted liraglutide for an OAD, indicating that liraglutide can be an effective addition when glycemic control fails with metformin.

Liraglutide was tested as triple therapy in LEAD-4 and -5, where it was used in combination with metformin and either rosiglitazone or glimepiride [23,24]. The greatest reductions in HbA_{1c} in any of the LEAD trials were when liraglutide was combined with metformin and rosiglitazone in LEAD-4 (-1.5% with both liraglutide doses) [23]. In combination with metformin and glimepiride in LEAD-5, liraglutide 1.8 mg was also significantly more effective than insulin glargine (-1.3 vs -1.1%; p = 0.0015) [24]. Together, these studies indicate that liraglutide is an effective addition to treatment when glycemic control cannot be maintained with two OADs.

In the two head-to-head trials with other incretin-based therapies, liraglutide proved to be more effective in the reduction of HbA_{1c} than both a DPP-4 inhibitor (sitagliptin) and an alternative GLP-1 RA (exenatide).

Reductions in HbA_{1c} in the 1860 trial, in which liraglutide 1.2 and 1.8 mg were compared with sitagliptin (all in combination with metformin) were 1.2 and 1.5% with liraglutide 1.2 and 1.8 mg, respectively, compared with 0.9% (p < 0.0001) with sitagliptin [26]. Reductions in HbA_{1c} with liraglutide were still superior to those with sitagliptin after 52 weeks of treatment in the trial extension: reductions were 1.3 and 1.5% for liraglutide 1.2 and 1.8 mg, respectively, compared with 0.9% for sitagliptin (p < 0.0001) [28]. The greater reductions with liraglutide are in line with the fact that GLP-1 RAs are provided at supraphysiological levels, whereas DPP-4 inhibitors can only increase GLP-1 to physiological concentrations.

In LEAD-6, once-daily liraglutide 1.8 mg was tested head-to-head with twice-daily exenatide as second- or third-line therapy in combination with metformin and/or glimepiride. The reduction in HbA_{1c} with liraglutide (1.1%) was significantly greater than with exenatide (0.8%; p < 0.0001) in the core trial period [25]. Patients who switched from exenatide to liraglutide in the trial extension experienced further significant reductions (0.32%; p < 0.0001), while patients who continued on liraglutide had relatively stable HbA_{1c} (reduction from 26 weeks of 0.06%) [27]. The improved efficacy of liraglutide compared with exenatide is primarily due to its prolonged duration of action; the maximal concentration of liraglutide is not reached until 8–12 h after dosing, and liraglutide has a plasma half-life of 13 h postadministration [101]. By comparison, exenatide twice-daily achieves median peak concentration in 2 h, with a terminal half-life of 2.4 h [102].

The benefits of liraglutide in control of HbA_{1c}, evident from the individual trials, are emphasized by the results of a meta-analysis of data from across the LEAD trials. The analysis revealed that liraglutide was effective in reducing HbA_{1c} regardless of baseline level, although greatest reductions were seen in patients with poorest initial control: a reduction of 2.5% was seen in patients whose baseline HbA_{1c} was >10.0% [30]. Additionally, *post hoc* analysis of 1860 trial data found that reductions in HbA_{1c} were greater with liraglutide 1.8 mg than with sitagliptin across baseline categories – reductions ranged from 0.9% for liraglutide 1.8 mg and 0.2% for sitagliptin in patients with baseline HbA_{1c} ≤7.5 to 2.3 and 1.4%, respectively, in patients with baseline HbA_{1c} >9% [31]. Together with individual trial results, this analysis indicates that liraglutide is effective across the disease spectrum.

Attainment of HbA_{1c} targets

The proportion of patients who met HbA_{1c} goals with liraglutide was assessed across the Phase III trials. Two internationally recognized goals were used: the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) consensus target of <7%, and the ≤6.5% target recommended by the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) [2,3]. Liraglutide was significantly more effective than comparators in bringing patients to both targets in all trials except LEAD-2, in which liraglutide was significantly more effective than metformin and comparable to glimepiride [20–26]. Overall, 35–58% of liraglutide-treated patients achieved the ADA target in the core Phase III trials (Figure 3 & Supplementary Table 1).

FPG

In all the core trials except LEAD-5 (in which liraglutide was compared with insulin glargine), liraglutide treatment resulted in reductions in FPG that were numerically greater than with comparators (Supplementary Table 1) [20–26]. Reductions ranged from 0.84 mmol/l with liraglutide 1.2 mg as monotherapy in LEAD-3, to 2.4 mmol/l with liraglutide 1.8 mg in combination with metformin and rosiglitazone in LEAD-4 [22,23]. All comparisons between liraglutide and placebo across the trials were statistically significant. Comparisons were also significant for both liraglutide 1.2 and 1.8 mg as monotherapy versus glimepiride (LEAD-3), for liraglutide 1.2 and 1.8 mg versus rosiglitazone (LEAD-1; in combination with glimepiride), for liraglutide 1.2 and 1.8 mg versus sitagliptin (1860; in combination with metformin) and for liraglutide 1.8 mg versus exenatide (LEAD-6; in combination with metformin and/or glimepiride) [20,22,25]. The significant advantages of liraglutide treatment over sitagliptin and glimepiride were further sustained for 1 and 2 years, respectively, in the 1860 and LEAD-3 extensions [28,29]. In the LEAD-6 extension, patients switching from liraglutide to exenatide had further significant reductions in FPG (0.9 mmol/l; p < 0.0001), while patients continuing on liraglutide had relatively stable levels (reduction of 0.2 mmol/l) [27].

Body weight

Patients treated with liraglutide 1.2 and 1.8 mg experienced significantly greater weight loss than patients treated with comparators in LEAD-2–5 and the 1860 study (Supplementary Table 1). Reductions ranged from 1 kg with liraglutide 1.2 mg as triple therapy in LEAD-4 to 3.4 kg with liraglutide 1.8 mg in combination with metformin in the 1860 study [23,26]. The significant weight loss compared with glimepiride in LEAD-2 indicates that there are advantages to using liraglutide rather than SU in combination with metformin, despite the similar effects of the two combinations on glycemic control [21].

The 2-year results of the LEAD-3 extension demonstrate that the weight loss experienced with liraglutide can be sustained – among patients who completed the extension, weight loss with liraglutide 1.2 and 1.8 mg was 2.1 and 2.7 kg, compared with a weight gain of 1.1 kg among patients treated with glimepiride (p < 0.0001) [29].

In LEAD-1, liraglutide was used in combination with SU, which is known to cause weight gain [2,20]. Body weight remained relatively stable with liraglutide

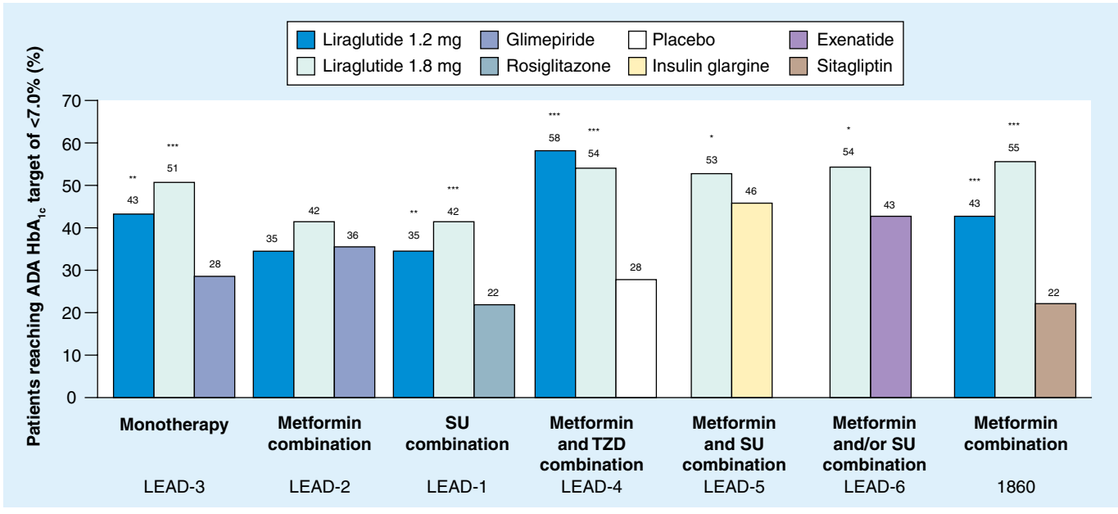

Figure 3. Proportion of patients achieving <7% American Diabetes Association glycosylated hemoglobin targets in the liraglutide Phase III studies.

*p < 0.02 versus comparator; **p < 0.001 versus comparator; ***p < 0.0001 versus comparator.

ADA: American Diabetes Association; SU: Sulfonylurea; TZD: Thiazolidinedione.

Data taken from [20–26].

(increase of 0.3 kg with liraglutide 1.2 mg, decrease of 0.2 kg with liraglutide 1.8 mg), which was significant compared with weight gain in rosiglitazone-treated patients (2.1 kg; p < 0.0001).

The head-to-head trials of liraglutide with incretin-based therapies are of particular interest when assessing body weight, as the positive effects of GLP-1 RAs and the neutral effects of DPP-4 inhibitors, are important features distinguishing incretin-based therapies from other treatments. Although DPP-4 inhibitors are generally thought of as weight-neutral [4], both liraglutide- and sitagliptin-treated patients lost weight in the 1860 study. However, after 26 weeks, weight loss was significantly greater with liraglutide (2.9 kg with liraglutide 1.2 mg, 3.4 kg with liraglutide 1.8 mg) than with sitagliptin (1 kg; p < 0.0001). This advantage of liraglutide over sitagliptin was maintained in the trial extension: after 1 year, weight loss with liraglutide 1.2 and 1.8 mg was 2.8 and 3.7 kg, respectively, compared with 1.2 kg with sitagliptin (p < 0.0001) [28].

In the LEAD-6 trial, liraglutide and exenatide were similarly effective in promoting weight loss: patients treated with liraglutide lost an average of 3.2 kg while those treated with exenatide lost 2.9 kg [25]. Notably, patients switching from exenatide to liraglutide in the LEAD-6 extension experienced significant further weight loss of 0.9 kg (p < 0.0001), as did patients who continued on liraglutide (0.4 kg; p = 0.0089) [27].

Meta-analysis of data from all of the LEAD trials emphasized the findings on body weight from the individual trials. Significant overall reductions in waist circumference were seen in patients using liraglutide (1.8 cm with 1.2 mg, 2.1 cm with 1.8 mg; p < 0.0001), as was the case with BMI (0.44 kg/m^2 with liraglutide 1.2 mg, 0.66 kg/m^2 with liraglutide 1.8 mg; p < 0.0001) [32]. Differences were greatest in patients with high baseline values, indicating that heavier patients are likely to experience the most weight-related benefit from liraglutide. Importantly though, a separate meta-analysis revealed that HbA_{1c} reductions in liraglutide treatment were independent of weight loss [33].

β-cell function

Preclinical and early clinical studies suggested that liraglutide may have a positive effect on the β-cell failure that underlies T2D [18,19]. However, in humans, direct measurement of β-cell function is problematic, and so the Phase III trials employed the indirect measures of HOMA-B and proinsulin:insulin ratio. Across the trials there was a trend towards improvement in β-cell function among liraglutide-treated patients, which was supported by the results of a meta-analysis of data from all LEAD trials [34]. The meta-analysis revealed significant increases in HOMA-B from baseline of 35.1 and 31.7% with liraglutide 1.2 and 1.8 mg, respectively (p < 0.0001). The increase was significant versus rosiglitazone (9.5%) for liraglutide 1.8 mg (p < 0.05) and versus placebo (7.4%) for both liraglutide doses (p < 0.0001; placebo encompasses arms from all trials and, therefore, a variety of treatments). The analysis also showed significant improvement from baseline in proinsulin:insulin ratio with both liraglutide 1.2 and 1.8 mg of −0.08 (p < 0.0001) – the decreases were significant versus rosiglitazone (−0.01), glimepiride (−0.02) and placebo (0.03) for both liraglutide 1.2 and 1.8 mg (p < 0.001 for all). Improvements in β-cell function (both HOMA-B and proinsulin:insulin ratio) were also observed in the 1860 study with both liraglutide 1.2 and 1.8 mg [26]. The results of these meta-analyses are supported by the longevity of the glycemic effects of liraglutide seen over 2 years in the LEAD-3 trial extension [29]; such long-term control is suggestive of maintenance of β-cell function. Taken together, these findings suggest that it may be useful to consider using liraglutide early in progression of T2D when there is most β-cell function to preserve.

SBP

Across the core trials, liraglutide reduced SBP from baseline by up to 6.7 mmHg (Supplementary Table 1) [20–26]. In all the LEAD trials, reductions with liraglutide were numerically greater than with comparators. Reductions reached significance with liraglutide 1.2 and 1.8 mg versus glimepiride in LEAD-2, with liraglutide 1.8 mg versus glimepiride in LEAD-3, with liraglutide 1.8 mg versus insulin glargine in LEAD-5, and with liraglutide 1.2 and 1.8 mg versus placebo in LEAD-4 [21–24].

These findings were confirmed by a meta-analysis of data from the LEAD trials, which showed significant decreases in SBP from baseline with liraglutide 1.8 and 1.2 mg (2.6 mmHg [p = 0.0008] and 2.5 mmHg [p = 0.003], respectively) [35]. The meta-analysis found that the full impact on SBP was evident after only 2 weeks of treatment, before major weight loss occurred, suggesting that the effect is independent of weight loss. The greatest reductions in SBP were observed in patients with the highest baseline SBP: the average reduction in patients with highest baseline SBP of >140 mmHg was 11.4 mmHg with liraglutide, compared with a reduction of 7.7 mmHg with placebo. An additional analysis revealed that the significant reductions in SBP from baseline were independent of concomitant antihypertensive treatment [36]. However, a minor increase in heart rate compared with baseline was observed in most of the LEAD trials following liraglutide treatment [37].

Lipids & cardiovascular markers

Lipid levels, as well as cardiovascular risk markers, were assessed as secondary end points across the Phase III trials. A meta-analysis of LEAD trial results revealed that there were significant reductions from baseline in patients treated with liraglutide 1.8 mg in total cholesterol (0.13 mmol/l), low-density lipoprotein-cholesterol (0.2 mmol/l), free fatty acids (0.09 mmol/l) and triglycerides (0.2 mmol/l; p < 0.01 for all), although these decreases were not significant compared with placebo or active comparators [38]. In addition, there were significant reductions from baseline in the cardiovascular risk markers brain natriuretic peptide (11.9%; p < 0.01) and high-sensitivity C-reactive protein (23.1%; p < 0.0001) [38]. A separate meta-analysis determined that treatment with liraglutide 1.8 mg significantly reduced levels of the cardiovascular risk marker plasminogen activator inhibitor-1 over 26 weeks (7.6%; p = 0.0008) [39]. These findings suggest that liraglutide may beneficially affect cardiovascular risk in addition to SBP, body weight and glycemic control.

Efficacy of liraglutide in Asian patients with T2D

The efficacy of liraglutide in Asian patients with T2D has been studied in three Phase III trials [40–42]. Two of the trials were conducted in Japanese patients and were similar in design to the LEAD-3 (1700 study; liraglutide monotherapy vs SU monotherapy [40]) and LEAD-1 trials (1701 study; liraglutide in combination with an SU vs SU monotherapy [41]); however, the maximum administered dose of liraglutide in the Japanese studies was 0.9 mg once daily. The third study (1796 study) was conducted in an Asian population from China, South Korea and India, and had a similar study design to LEAD-2 – liraglutide (0.6, 1.2 and 1.8 mg) versus SU, both in combination with metformin [42].

In line with the results from the LEAD-3 trial, liraglutide monotherapy in Japanese patients with T2D resulted in a significantly greater reduction in HbA_{1c} compared with SU monotherapy (-1.9 vs -1.4%, respectively; p < 0.0001), and improvement in body weight (-0.92 vs +0.99 kg, respectively; p < 0.0001) [40]. In the 1701 study, patients randomized to receive liraglutide (either 0.6 or 0.9 mg) as an addition to SU monotherapy had significantly greater decreases in HbA_{1c} compared with those who received placebo (-1.46 and -1.56 vs -0.40%, respectively; p < 0.0001 for both doses of liraglutide vs placebo) [41]. Consistent with results from the LEAD-1 trial, the use of liraglutide (0.6 and 0.9 mg) in combination with an SU negated the weight benefits of liraglutide (weight change +0.06 and -0.37 kg, respectively) although, a

significant reduction in weight was observed in the placebo group receiving SU monotherapy (-1.12 kg) [41]. The changes in HbA_{1c} and body weight observed at week 24 in both these Japanese studies were maintained at week 52 [43,44], also consistent with the LEAD-1 and LEAD-3 studies.

Data from the 16-week 1796 study are also consistent with those from Caucasian patients (LEAD-2) [42]. The use of liraglutide (1.2 or 1.8 mg) or glimepiride in combination with metformin resulted in similar improvements in HbA_{1c} (-1.36, -1.45 and 1.39%, respectively). However, as seen in LEAD-2, patients taking liraglutide had greater weight loss and less frequent hypoglycemia than patients taking glimepiride. Reported improvements in β-cell function (which were similar with liraglutide and glimepride) and SBP (significantly greater with liraglutide vs glimepirirde) were also in accordance with those from LEAD-2 [42].

These data suggest that the clinical efficacy of liraglutide is similar in Asian and Caucasian patients with T2D. The use of liraglutide 1.2 and 1.8 mg was well tolerated in an Asian population, suggesting that these doses may also be transferable to Japanese patients [42].

Composite end points: measurement of clinically relevant variables

Treatment of T2D is a multifaceted challenge: in addition to hyperglycemia, patients are often overweight and suffer from hypertension and dyslipidemia. To assess the broader benefits of liraglutide treatment, the proportions of patients in the Phase III trials meeting two composite end points were assessed.

■ HbA_{1c} <7.0% with SBP <130 mmHg & no weight gain

This first end point was designed to address variables considered in the standards of care recommended by the ADA [45]. A meta-analysis approach was used to determine the proportion of patients in the LEAD-1–6 trials achieving this triad after 26 weeks of treatment [46]. The end point was achieved by 26% of patients taking liraglutide 1.8 mg and 22% of patients taking liraglutide 1.2 mg. The odds ratios for achieving the composite end point were significantly improved for patients taking liraglutide 1.8 mg than among patients randomized to comparator treatments (Figure 4; $p < 0.02$ for all) [46].

■ HbA_{1c} <7.0% with no hypoglycemic events & no weight gain

The proportion of patients achieving a second composite end point was also assessed using meta-analysis of data from the LEAD trials. This end point was achieved by 39% of patients taking liraglutide 1.8 mg and 32% taking liraglutide 1.2 mg [47]. Again, the odds ratios for achieving this end point were significantly improved for patients taking liraglutide 1.8 mg than comparator treatments ($p < 0.005$ for all; Figure 4). This second end point was also as prespecified in the 1860 trial, where it was achieved by 46 and 37% of patients taking liraglutide 1.2 or 1.8 mg, respectively, compared with 14% of patients taking sitagliptin ($p < 0.0001$) [26].

Taken together, the findings from analyses of these two composite end points indicate that liraglutide can be useful in limiting the challenges commonly associated with T2D and its treatment.

Treatment satisfaction

Health-related quality of life of patients with T2D is lower than that of the general population [48]. Factors including glycemic control, presence of diabetic complications and the complexity of treatment regimens can affect quality of life [48,49]. Patient perception of treatment and effects on quality of life are important in determining effectiveness of any therapeutic agent, and so in four of the liraglutide trials, LEAD-2, -3, -6 and 1860, patient satisfaction was assessed.

In LEAD-3, in which liraglutide and glimepiride monotherapy were compared, a validated self-administered, 77-point questionnaire was used to assess weight perception, psychological wellbeing and overall quality of life [50]. In line with the fact that patients tended to gain weight with glimepiride and lose weight with liraglutide, patients treated with liraglutide 1.8 mg were 52% less likely to feel overweight than patients treated with glimepiride. Overall patient assessment of weight, compared with the reference point 'my weight is just right', was more favorable with liraglutide 1.8 mg than with glimepiride (score of 40 with liraglutide 1.8 mg vs 48.7 with glimepiride; $p < 0.002$). Importantly, mental and emotional health, as well as general perception of health, also improved more with liraglutide 1.8 mg than with glimepiride.

In LEAD-2, -6 and the 1860 trial, patient satisfaction was assessed using the Diabetes Treatment Satisfaction Questionnaire (DTSQ) [51–53]. Clinical outcomes from the LEAD-2 trial (in which liraglutide was compared with glimepiride, both in combination with metformin) have been fully reported from the core 26-week trial period, but data on patient-reported outcomes are available from both the core trial and an 18-month extension period. Results at 26 and 78 weeks indicated an improvement in overall treatment satisfaction that was comparable in patients treated with liraglutide and glimepiride: at 26 and 78 weeks, respectively, scores were 12.5 and

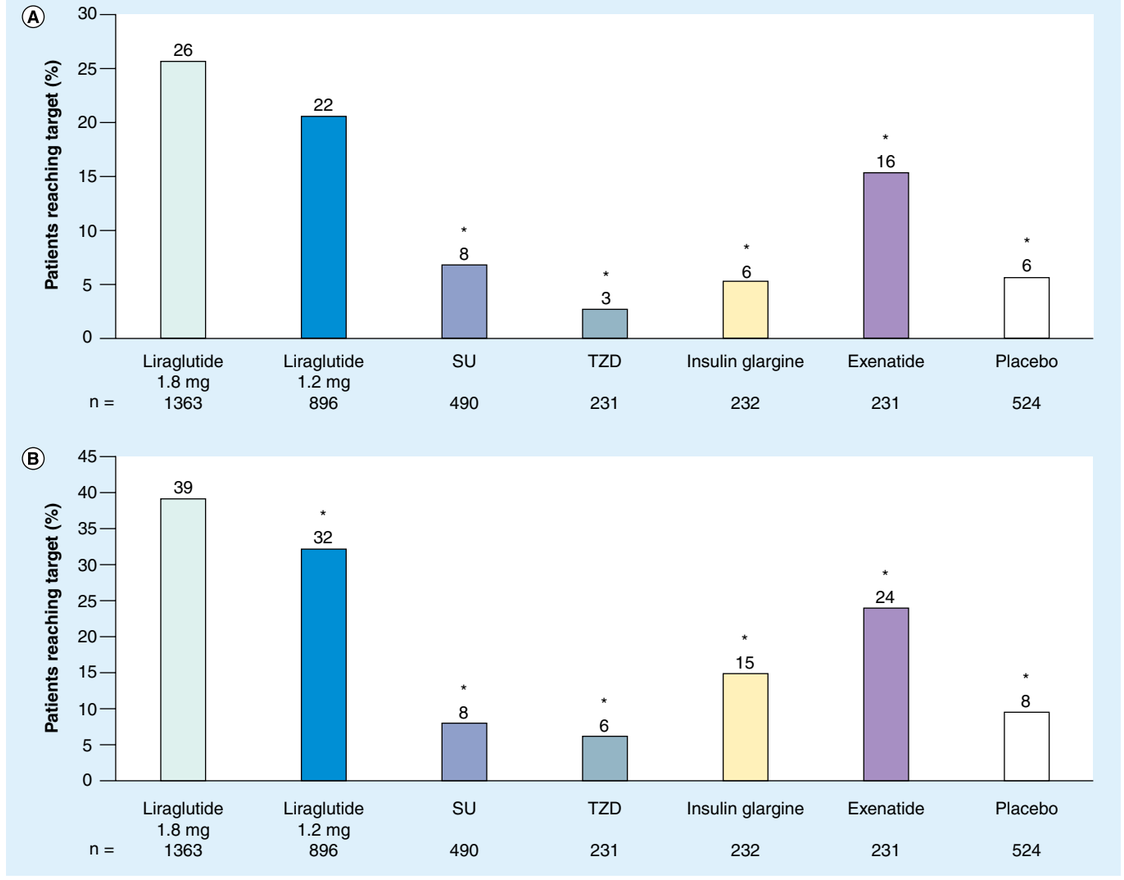

Figure 4. Patients achieving composite end points in the LEAD trials. (A) HbA_{1c} <7%, no weight gain, systolic blood pressure <130 mmHg. **(B)** HbA_{1c} <7%, no weight gain, no hypoglycemia.
*$p < 0.02$ versus liraglutide 1.8 mg.
SU: Sulfonylurea; TZD: Thiazolidinedione.
Data taken from [46,47].

12.4 for liraglutide 1.2 mg, 10.9 and 10.8 for liraglutide 1.8 mg, and 11.7 and 11.6 for glimepiride. After week 26, the trial was unblinded, and so was a direct comparison of an injectable and an oral treatment. The fact that patients injecting liraglutide had similar improvement in treatment satisfaction to patients taking glimepiride is a strong indicator that injection with liraglutide does not negatively affect patient perceptions and acceptance of treatment.

In head-to-head trials of liraglutide with other incretin-based therapies, liraglutide resulted in significantly greater improvements in treatment satisfaction than the comparators [52,53]. In the LEAD-6 trial, the change in overall treatment satisfaction after 26 weeks was significantly greater with liraglutide (4.7) than with exenatide (1.7; $p < 0.0001$), with significant improvements recorded in five of the six individual items assessed (current treatment, convenience, flexibility, recommend and continue); the difference in treatment satisfaction in this instance is notable as both therapies are in the same treatment class. In the comparison between liraglutide and sitagliptin, there was greater improvement in treatment satisfaction score over 26 weeks with liraglutide 1.8 mg (4.4) than with sitagliptin (3.5; $p = 0.03$). That liraglutide resulted in greater treatment satisfaction

than sitagliptin again suggests that injection need not be a barrier to treatment with liraglutide.

Overall, these findings suggest that the need for injection with liraglutide does not impair patient satisfaction, and that liraglutide compares favorably in terms of patient perceptions with other available T2D treatments.

Safety & tolerability of liraglutide

Liraglutide was found to be well tolerated across the Phase III trial program. The incidence of hypoglycemia, which is of particular interest with therapies that control glycemia, was found to be low with liraglutide treatment. Of 2739 patients treated with liraglutide in the core trials, only seven experienced episodes of major hypoglycemia (defined as blood glucose <3.1 mmol/l and requiring third-party assistance). Minor hypoglycemia (blood glucose <3.1 mmol/l) also occurred infrequently with liraglutide, especially when used without SUs. Rates ranged from 0.03 events/subject year with liraglutide in combination with metformin (LEAD-2) to 1.93 events/subject year in combination with metformin and/or glimepiride (LEAD-6) [20–25].

Gastrointestinal side-effects, which have been found to be common with GLP-1 RAs [101,102], were among the most frequently reported adverse events with liraglutide. In most trials, the most common gastrointestinal effect was nausea. The proportion of patients experiencing nausea ranged from <11.0% with liraglutide 1.2 and 1.8 mg in LEAD-1 (in combination with glimepiride) to 40.0% with liraglutide 1.8 mg in LEAD-4 (in combination with metformin and rosiglitazone) [20,23]. Nausea was generally more common than with comparators, although, in most cases, nausea was transient and decreased after the first weeks of treatment [20–26]. In LEAD-6, when liraglutide was compared with exenatide, the incidence of nausea tended to be less persistent with liraglutide than with exenatide [25], which may have been a contributing factor to the greater treatment satisfaction experienced by patients taking liraglutide.

The cardiovascular safety of liraglutide has been reported in a pooled analysis of data from all Phase II and III studies from the liraglutide developmental program [54]. The incidence of major adverse cardiovascular events with liraglutide was lower than with all comparators (ratio 0.73) and within the US FDA cardiovascular safety limits.

T2D is the leading cause of renal impairment due to inadequate glycemic control [55]. A meta-analysis of data from the LEAD studies reported that liraglutide treatment was safe and well tolerated in patients with mild renal impairment; there was no significant difference in creatinine clearance between liraglutide-treated patients with mild renal impairment compared with those with normal renal function [56]. Furthermore, mild renal impairment did not affect HbA_{1c} reductions or frequency of nausea in liraglutide-treated patients, compared with those with normal renal function.

There has been some discussion about the potential for pancreatitis with GLP-1 RA treatment. Incidence of pancreatitis was monitored across the Phase III trials; only nine cases of acute pancreatitis were reported with liraglutide (<0.2%), compared with one case with a comparator (1.7 vs 0.7 cases per 1000 patient-years for liraglutide vs comparators) [101]. Calcitonin levels were also monitored during the Phase III trials, due to the fact that, in early preclinical trials in rats and mice, liraglutide was found to increase the incidence of C-cell carcinoma [57]. GLP-1 RAs were shown to stimulate calcitonin release and, following long-term exposure, C-cell hyperplasia in rats [57]. By contrast, 20 months of liraglutide treatment (at >60-times human exposure levels) in cynomolgus monkeys had no effect on plasma calcitonin levels, and C-cell hyperplasia was not detected. No patients receiving liraglutide in the LEAD program developed C-cell carcinoma and an analysis of calcitonin levels among patients exposed to liraglutide for 2 years in clinical trials showed that average calcitonin levels remained at the lower end of the normal range [57].

Use of liraglutide in clinical practice

The Phase III trials have demonstrated the clinical potential of liraglutide across the continuum of T2D. Liraglutide has been shown to be effective in providing glycemic control, in a range of treatment combinations. As well as glycemic control, liraglutide was found to provide a reduction in body weight and SBP, as well as improvements in β-cell function. With these additional benefits over traditional therapies, liraglutide is an attractive option for the management of T2D.

Because liraglutide has been tested in a wide range of different treatment combinations, there is strong evidence to support its use at different stages of disease progression. However, approved indications differ between countries and regions. In Europe and the USA, for example, both 1.2 and 1.8 mg doses of liraglutide are approved for use, but use as monotherapy is only indicated in the USA [103,104]. In Europe, liraglutide is approved for use as dual or triple therapy in combination with OADs [103]. Specifically, the European Medicines Agency states that liraglutide may be used as dual therapy in addition to metformin or SU if glycemic control is inadequate with either treatment as monotherapy, and it may be used in triple therapy with metformin and SU/TZD if glycemic control is insufficient with dual therapy [103].

Although some local guidelines for treatment of T2D now make specific reference to liraglutide (e.g., those in the UK and Denmark) [105,106], internationally recognized treatment algorithms, such as those produced by the ADA/EASD [2] and AACE/ACE [3], include guidance on GLP-1 RAs that is specifically linked to exenatide as they were written before the approval of liraglutide. As liraglutide is now approved for use in >30 countries worldwide, it is likely that the next editions of these treatment algorithms will include specific guidance on liraglutide, and affirm its place in the T2D treatment continuum.

Future perspective

The Phase III trial program demonstrated that liraglutide provides effective glycemic control, alongside reductions in body weight and SBP. In addition, liraglutide beneficially affects measures of β-cell function, as well as lipid levels and cardiovascular risk markers. These benefits are provided along with a low rate of hypoglycemia and good tolerability. Liraglutide is now approved for use across the world and it will be of interest to observe how liraglutide performs in real-life clinical practice as audit data become available.

It will be of particular interest to observe how liraglutide performs with long-term use, especially when treatment is started in patients in earlier disease stages, where there is potential to preserve β-cell function. Although it should be noted that liraglutide is not universally approved as a monotherapy, the recently published results from the 2-year extension of the LEAD-3 trial of liraglutide as monotherapy provide an indication that liraglutide can be effective in the long term in patients who have not progressed to advanced stages of diabetes therapy [29]. Results from 2-year extensions of the LEAD-2 and 1860 trials are expected soon, and will also be relevant in understanding the long-term benefits of liraglutide.

Two trials that are yet to be fully reported will be important in determining the eventual place of liraglutide in the treatment of T2D. One trial is designed to test the addition of insulin to treatment with liraglutide and metformin. This is a treatment avenue that holds promise for patients in advanced stages of T2D, and results reported so far show that the combination can improve glycemic control [58]. Recent results indicate that exenatide can also improve glycemic control when combined with insulin [59]. The second trial, which is still ongoing, is the LEADER trial, which was designed to assess cardiovascular outcomes [60]. Results will be important in confirming the cardiovascular safety of liraglutide. Given that GLP-1 itself appears to have cardioprotective effects, and that the LEAD trials suggest positive effects of liraglutide on cardiovascular biomarkers, the results are awaited with interest.

Supplementary data

Supplementary data accompanies this paper and can be found at www.future-science.com/doi/suppl/10.4155/CLI.11.166

Executive summary

Incretin-based therapies in Type 2 diabetes

- Chronic hyperglycemia is the characteristic feature of Type 2 diabetes (T2D), and improved glycemic control is the primary aim of treatment.
- A wide range of therapies are available for management of hyperglycemia in T2D, but many treatments have the undesirable side effects of weight gain and hypoglycemia.
- The recently developed glucagon-like peptide (GLP)-1 receptor agonists (RAs) can effectively manage hyperglycemia without weight gain or hypoglycemia.

Liraglutide

- Liraglutide is a GLP-1 RA, with 97% amino acid identity to native GLP-1.
- An extensive program of Phase III clinical trials has demonstrated that liraglutide can effectively and safely manage hyperglycemia across the continuum of care in T2D.

Efficacy of liraglutide

- In addition to reducing hyperglycemia, liraglutide provides the additional benefits of reduction in body weight and systolic blood pressure, as well as improvements in measures of β-cell function.
- When compared directly with other incretin-based therapies – the dipeptidyl peptidase-4 inhibitor sitagliptin and the GLP-1 RA exenatide – liraglutide performs favorably in terms of glycemic control. Weight loss is similar with liraglutide and exenatide, but significantly greater with liraglutide than sitagliptin.

Safety & tolerability of liraglutide

- Liraglutide is generally well tolerated; the most common side-effects are gastrointestinal, and these are generally mild and transient.

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