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Liraglutide

A Review of its Use in the Management of Type 2 Diabetes Mellitus

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Data Selection

Sources: Medical literature (including published and unpublished data) on liraglutide was identified by searching databases (including MEDLINE, EMBASE) for articles published since 1996, bibliographies from published literature, clinical trial registries/databases and websites (including those of regional regulatory agencies and the manufacturer). Additional information (including contributory unpublished data) was also requested from the company developing the drug.

Search strategy: MEDLINE, EMBASE and AdisBase search terms were 'liraglutide' and ('type-2 diabetes mellitus' or 'diabetes mellitus, type 2' or 'non insulin dependent diabetes mellitus'). Searches were last updated 2 November 2011.

Selection: Studies in patients with type 2 diabetes mellitus who received liraglutide. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Liraglutide, glucagon-like peptide 1 analogues, GLP-1, incretin therapies, type 2 diabetes mellitus, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability, bodyweight loss.

Contents

Abstract

Liraglutide (Victoza®) is a subcutaneously administered glucagon-like peptide-1 (GLP-1) receptor agonist produced by recombinant DNA technology and used as an adjunct to diet and exercise in the treatment of adults with type 2 diabetes mellitus. This article reviews the clinical efficacy and tolerability of liraglutide in adults with type 2 diabetes, and provides a summary of its pharmacological properties. Recently published pharmacoeconomic studies of liraglutide are also reviewed.

Administered subcutaneously, liraglutide (usually 1.2 or 1.8 mg once daily) generally produced greater improvements in glycaemic control than active comparators or placebo when administered as monotherapy or in combination with one or two oral antidiabetic drugs (OADs) to adults with type 2 diabetes in numerous randomized, controlled phase III trials. These included six trials in the LEAD trial programme that was designed to evaluate the efficacy and safety of liraglutide across a continuum of antihyperglycaemic management for patients with type 2 diabetes.

Liraglutide was generally well tolerated, with a low risk of hypoglycaemia evident, in the phase III trials. The most common adverse events were gastrointestinal and included nausea and diarrhoea; most events were mild to moderate in severity and decreased in incidence over time.

In conclusion, liraglutide has an important place in the management of adults with type 2 diabetes across a continuum of care. As well as providing effective glycaemic control, liraglutide improves pancreatic β-cell function and leads to bodyweight loss, thereby addressing some of the unmet needs of patients treated with traditional OADs.

1. Introduction

Type 2 diabetes mellitus is a major health problem worldwide. The rapid increase in the prevalence of type 2 diabetes over recent years has been attributed to a growing ageing population, and to increases in overweight and obese populations at particular risk of developing the disease. It has been estimated that 366 million people worldwide will have developed type 2 diabetes by 2030.[1,2] Control of hyperglycaemia in patients with type 2 diabetes is a major goal of treatment, as this has been shown to reduce microvascular complications, macrovascular problems (coronary events) and improve health outcomes.[3,4]

Although many drugs are effective in terms of achieving glycaemic control in type 2 diabetes, most traditional treatments do not address the decline in pancreatic function; moreover, several drugs lead to bodyweight gain, a particular problem in patients who are often already overweight or obese. New drugs addressing these issues and also providing benefits in terms of their cardiovascular profile are therefore being evaluated in the clinical setting.

The incretin hormones have multiple physiological effects and play an important role in glucose homeostasis. Glucagon-like peptide-1 (GLP-1) is an endogenous incretin hormone produced by intestinal cells that has a major function in the maintenance of normoglycaemia, potentiating insulin secretion from the pancreatic β cells when glucose is taken orally; this is known as the 'incretin effect', an effect that is blunted in patients with diabetes (reviewed by Croom and McCormack[5] and Gallwitz[6]). Although human native GLP-1 theoretically has potential in the treatment of patients with diabetes, it is rapidly degraded by dipeptidyl peptidase-IV (DPP-4) and has a short half-life of about 1.5–2.5 minutes, meaning that it would have to be given by continuous infusion to be of clinical use. To overcome these limitations, longer-acting analogues of GLP-1, including liraglutide (Victoza®) and exenatide, have been developed for use in the treatment of patients with type 2 diabetes.[5]

This article reviews the clinical efficacy and tolerability of liraglutide in adults with type 2 diabetes, and provides a summary of its pharmacological

properties. Recently published pharmacoeconomic studies of liraglutide are also reviewed.

2. Pharmacodynamic Properties

The pharmacodynamic properties of liraglutide have been reviewed previously in detail in *Drugs*.[5] Liraglutide is an acylated GLP-1 analogue, produced by recombinant DNA technology in *Saccharomyces cerevisiae*, in which Arg 34 replaces Lys 34 at the *N*-terminal and a fatty acid chain is added to Lys 26. Liraglutide has 97% amino acid sequence identity (homology) to human endogenous GLP-1 (7-37), which accounts for <20% of total circulating endogenous GLP-1.[7,8] Liraglutide binds to and activates the GLP-1 receptor, a membrane-bound cell-surface receptor coupled to adenylyl cyclase by the stimulatory Gs G-protein in pancreatic β cells and the target for endogenous GLP-1. This results in increases in intracellular cyclic adenosine monophosphate (cAMP) and subsequent liraglutide dose-dependent insulin release in patients with elevated glucose levels. Concurrently, inappropriately high glucagon secretion is decreased by liraglutide in a glucose-dependent fashion, thereby blocking the effects of glucagon on hepatic glucose output. In the presence of liraglutide, as blood glucose concentrations decrease, the secretion of insulin diminishes and blood glucose concentrations approach euglycaemia. In addition to these glucoregulatory mechanisms, liraglutide produces a minor delay in gastric emptying, and decreases bodyweight and body fat mass by reducing hunger and lowering energy intake; these effects contribute to the beneficial effects of the drug in patients with type 2 diabetes.[7,8] A summary of the pharmacodynamic properties of liraglutide in patients with type 2 diabetes, supported by data from animal and *in vitro* studies, is presented in table I.

Table I. Summary of the pharmacodynamic properties of liraglutide: results of studies in adults with type 2 diabetes mellitus, supported by data from animal studies and *in vitro* investigations[5,7-51]

Reduces glycosylated haemoglobin levels
Reduces fasting and postprandial plasma glucose levels
Produces sustained improvements in glucose levels over a 24-hour dosage interval after subcutaneous administration
Increases insulin secretion
Reduces postprandial glucagon secretion
Delays gastric emptying
Increases satiety
Improves β-cell function
Reduces bodyweight
Reduces body mass fat
Improves some biomarkers of cardiovascular risk
Reduces systolic blood pressure
Does not produce clinically relevant increases in calcitonin levels
Associated with a low incidence of anti-liraglutide antibodies

When liraglutide is administered as a subcutaneous injection once daily, dose-dependent reductions in both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) levels occur over a 24-hour period in patients with type 2 diabetes. Decreases in bodyweight and improvements in some biomarkers of cardiovascular disease have also been widely reported in clinical trials of the drug.[5,7,8] Glycosylated haemoglobin (HbA_{1c}), FPG levels and other glycaemic endpoint results reported in clinical trials of subcutaneously administered liraglutide in adults with type 2 diabetes are reviewed in section 4, together with results related to the effects of liraglutide on bodyweight, systolic blood pressure (SBP) and other efficacy endpoints.

Improved β-cell function was widely reported in the major clinical trials of liraglutide in patients with type 2 diabetes (section 4) and preservation of β-cell function with liraglutide, achieved via suppression of β-cell apoptosis as well as β-cell neogenesis and proliferation, has been observed in animal studies.[50] Consistent with the hormonal effects of GLP-1 on the gastrointestinal system, liraglutide slowed gastric emptying in patients with type 2 diabetes. Persistent and marked anorectic effects that led to weight loss were produced in animals.[47] In addition, inhibition of β-cell mass increases associated with obesity resulting in the normalization of weight and fat mass were observed in animal models of obesity.[52]

Serum calcitonin is a biomarker for various C-cell diseases, including medullary thyroid carcinoma (MTC) and hereditary C-cell hyperplasia (CCH).[49] Several GLP-1 analogues, including liraglutide and exenatide, were shown to activate

thyroid C cells in rodents, resulting in calcitonin release, upregulation of calcitonin gene expression and proliferation of C cells.[48] By contrast, in primates, calcitonin release was not generated by liraglutide at high systemic exposures, nor was there evidence of C-cell hyperplasia.[48]

Despite the reported association between liraglutide and CCH, C-cell carcinomas and C-cell adenomas in rats, evidence from >5000 patients with type 2 diabetes treated with various dosages of liraglutide in large, randomized trials (section 4) suggests that effects observed in rodents may not apply to humans, as sustained liraglutide treatment did not lead to increases in calcitonin levels in adults with type 2 diabetes.[48,49] In 609 patients receiving liraglutide treatment for 2 years in the LEAD (Liraglutide Effect and Action in Diabetes)-2 and LEAD-3 trials (section 4), geometric mean calcitonin levels of ≈1 pg/mL or lower at all evaluations were sustained at the lower end of the normal range of ≤8.4 pg/mL in men or ≤5.0 pg/mL in women. When data from a further nine clinical studies of ≥20 weeks' duration were combined with these study results, no treatment-related differences between recipients of liraglutide, active comparator or placebo were observed in the proportions of patients with clinically relevant serum calcitonin levels of >20 pg/mL (≤ 0.3% across liraglutide, active comparator and placebo groups at week 104).[48] In another study, serum calcitonin levels in liraglutide recipients were measured at baseline and every 12 weeks thereafter for up to 2 years.[49] Basal mean calcitonin levels were towards the lower end of the normal range and remained well below the upper level of normal for the duration of the trials, with a small proportion of patients (≤1.67%) developing clinically relevant serum calcitonin levels of >20 ng/L up to 104 weeks after the start of treatment.[49]

Clinical evidence has shown a decrease in the efficacy of GLP-1 receptor agonists as a result of the induction of anti-GLP-1 receptor agonist antibodies. The extent of antibody induction appears to be related to the homology of the GLP-1 receptor agonist, with ≈50% of recipients of exenatide (53% homology) developing anti-exenatide antibodies, which can decrease the efficacy of the drug in patients with type 2 diabetes.[51,53] By contrast, liraglutide has high (97%) homology, inducing anti-liraglutide antibodies at low titres (in <10% of patients) that do not appear to appreciably reduce its efficacy in patients with type 2 diabetes (section 5).[14,51]

Liraglutide 0.6, 1.2 or 1.8 mg once daily produced no clinically relevant prolongation in the corrected QT interval in 51 healthy participants, in a randomized, placebo-controlled, double-blind, crossover study.[54] The presence of mild renal impairment did not affect the efficacy of liraglutide in patients with type 2 diabetes in a meta-analysis of data from six randomized trials in the LEAD programme (section 4).[55]

3. Pharmacokinetic Properties

A summary of the pharmacokinetic profile of liraglutide is presented in table II.

After subcutaneous injection, the fatty acid side chain of liraglutide allows it to self-associate and form heptamers that bind to interstitial albumin at the injection site.[56-58] As a result, liraglutide is absorbed slowly,[56-58] with maximum plasma concentrations (C_{max}) achieved 8–12 hours after subcutaneous administration,[7] allowing for once-daily administration.[59-61] After a single 0.6 mg subcutaneous dose, estimated mean C_{max} values were 35 ng/mL[8] and 9.4 nmol/L,[7] and the area under the plasma concentration-time curve (AUC) was 960 ng • h/mL.[8] Systemic exposure to liraglutide increases proportionally with dose;[7] liraglutide C_{max} and AUC values increased proportionally over the 0.6–1.8 mg dose range.[8]

Table II. Summary of the pharmacokinetic profile of liraglutide after single or once-daily subcutaneous administration in adults with type 2 diabetes mellitus or healthy adult volunteers[5,7,8]

Slow absorption
Linear dose-proportional systemic exposure
Absolute bioavailability ≈55%
Mean apparent volume of distribution 11–17 L
Extensive (>98%) plasma protein binding
Metabolism similar to that of large proteins
Eliminated as unchanged drug
Mean apparent clearance ≈1.2 L/h
Elimination half-life ≈13 h
Low potential for clinically relevant drug interactions

Dose-dependent increases in liraglutide AUC from time zero to 24 hours, C_{max} and trough plasma liraglutide concentrations were observed in healthy Japanese individuals who received multiple doses (up to 25 μg/kg) of subcutaneously administered liraglutide once daily in a dose-escalation study.[62] The mean steady-state liraglutide concentration over 24 hours after a 1.8 mg dose of liraglutide was ≈128 ng/mL[8] or ≈34 nmol/L.[7] After single-dose administration, the intra-subject coefficient of variation for the AUC of liraglutide was 11%.[7] The AUC from time zero to infinity (AUC_∞) of liraglutide after subcutaneous injection into the thigh was 22% lower than that after injection into the abdomen, whereas the AUC_∞ after injection into the upper arm was equivalent to that after subcutaneous injection into the abdomen or thigh.[8] Nevertheless, systemic exposure to liraglutide is considered comparable for these injection sites and so these sites can be used interchangeably by patients receiving treatment with the drug.[7,8,63]

The mean apparent volume of distribution of liraglutide is ≈13 L (after subcutaneous administration of liraglutide 0.6 mg)[8] or 11–17 L.[7] Liraglutide is extensively (>98%) bound to plasma proteins.[7,8] Liraglutide is metabolized in a manner similar to that of large proteins, with no specific organ identified as a major route of elimination.[7,8] *In vitro*, liraglutide undergoes metabolism by DPP-4 and neutral endopeptidase, and evidence from *in vivo* studies suggests that this also occurs in humans, although this process is slower than with native GLP-1.[5] After single-dose administration of [^{3}H]-liraglutide to healthy volunteers, the major component identified in plasma during the initial 24 hours was intact liraglutide.[7,8] Two minor metabolites were also detected and accounted for ≤9% and ≤5% of total plasma radioactivity exposure.[7] After administration of a dose of [^{3}H]-liraglutide, a minor portion of administered radioactivity was excreted as liraglutide-related metabolites in the faeces (5%) or urine (6%) during the first 6–8 days.[7,8] No intact liraglutide was detected in the faeces or urine.[7] Following subcutaneous single-dose administration of liraglutide, the mean apparent clearance of liraglutide was ≈1.2 L/h. The fatty acid portion of liraglutide allows the drug, as a monomer, to bind to serum albumin[56] and resist degradation by DPP-4, thereby prolonging its elimination.[60] Indeed, the elimination half-life of liraglutide is about 13 hours, allowing for once-daily subcutaneous administration.[7,8] Studies in small numbers of patients with type 2 diabetes have shown that the pharmacokinetic profile of liraglutide is not substantially altered in individuals with renal[64] or hepatic impairment.[7,8,65]

Liraglutide has a low potential for pharmacokinetic interactions mediated via cytochrome P450 or relating to plasma protein binding displacement.[7,8] Although the slight prolongation in gastric emptying with liraglutide may affect the extent of absorption of co-administered drugs, studies have shown an absence of clinically relevant interactions between subcutaneous liraglutide 1.8 mg once daily and single doses of paracetamol (acetaminophen), atorvastatin, griseofulvin, digoxin, lisinopril or oral contraceptives.[7,8,66,67] In all studies, the timing of the co-administered drug was such that the C_{max} of liraglutide would coincide with the C_{max} of the co-administered drugs.[7,8] At steady state, liraglutide 1.8 mg once daily and single-dose subcutaneous insulin detemir 0.5 U/kg did not interact in a pharmacokinetic manner in patients with type 2 diabetes, although additive pharmacodynamic effects were observed.[68] Of note, liraglutide is not approved for use in combination with insulin or insulin substitutes/analogues.[7,8] However, the European Committee for Medicinal Products for Human Use has adopted a positive opinion on the use of insulin detemir as add-on therapy to liraglutide in combination with metformin in patients with type 2 diabetes.[69] When warfarin is administered to patients receiving liraglutide, more frequent monitoring of the international normalized ratio is recommended, as any potential interaction between the two drugs has not yet been evaluated.[7]

4. Therapeutic Efficacy

The therapeutic efficacy of subcutaneous liraglutide administered once daily as monotherapy or in combination with one or two oral antidiabetic drugs (OADs) has been evaluated in

numerous phase III clinical trials in adults with type 2 diabetes.[9-13,15,16,19-22,24,70-72] Earlier short-term studies in adults with type 2 diabetes showed that various, including nonapproved, dosages of liraglutide improved glycaemic control, with no evidence of bodyweight gain or major tolerability issues.[43,44,73,74] These studies in part formed the basis for the phase III programme but are not reviewed further in this article.

The duration of most of the phase III trials was 26 weeks, although longer term efficacy data (up to 2 years for monotherapy) have also been published. Most trials were conducted as part of the recent phase III LEAD trial programme. The LEAD programme included five randomized, double-blind trials and one randomized, open-label trial, and enrolled more than 6 500 patients recruited from more than 600 sites across 41 countries worldwide. The main aim of this programme was to evaluate the efficacy of liraglutide compared with both placebo and commonly used active comparators from three drug classes across a continuum of standard management for patients with type 2 diabetes. Comparators in the double-blind trials included rosiglitazone, glimepiride and insulin glargine.[11,12,16] In the open-label LEAD-6 trial, liraglutide was compared with exenatide over 26 weeks,[13] with the efficacy of liraglutide assessed for a further 14 weeks in exenatide-treated patients who switched to liraglutide at week 26.[70] Dosages of study drugs in the LEAD studies were attained during an initial forced-titration period of 2–3 weeks after randomization.

Table III. General inclusion and exclusion criteria in randomized, comparative trials of liraglutide, including the LEAD studies, in adult patients with type 2 diabetes mellitus

Inclusion criteria
Age 18–80 y[9-13,15,16,19,21,22,24]
Baseline glycosylated haemoglobin 7–10% or 7–11%[9-13,15,16,19,21,22,24]
Body mass index ≤40 or ≤45 kg/m^2 [9-13,15,16,19,22,24]
Exclusion criteria
Previous insulin therapy (with the exception of short-term treatment) within 3 months or at any other time[9-13,15,16,19,22,24]
Hepatic or renal impairment[9-11,13,16,19,24]
Uncontrolled hypertension (≥180/100 mmHg)[11,13,16,24]
Clinically significant cardiovascular disease[13,16,19,24]

Several other randomized, placebo- and active-comparator trials of liraglutide have been conducted. These include a 26-week open-label study comparing liraglutide with sitagliptin (a DPP-4 inhibitor),[19] with 52-week follow-up,[20] and several studies in Asian populations.[21,22,24,71,72] Studies evaluating the efficacy of liraglutide administered at dosages currently approved in the EU and US are the main focus of this section.

General inclusion and exclusion criteria in the large, randomized trials reviewed are summarized in table III. Other study design details, including primary endpoints and the main secondary endpoints, are presented in table IV. In most cases, analyses were conducted on the intent-to-treat population, with hierarchical testing for non-inferiority and superiority performed on glycaemic endpoint results in some studies.

4.1 Monotherapy

The efficacy of liraglutide as monotherapy has been evaluated in several studies,[24,43,44,72-74] including LEAD-3,[9,10] the largest monotherapy study and main focus of this section. Study participants in LEAD-3 were regarded as having early-stage type 2 diabetes, as they were being managed with lifestyle modification (≈36% of randomized patients) or did not have adequate glycaemic control with a single OAD administered at a dose that was <50% of the maximum approved dose.[9]

Patients were initially randomized to receive liraglutide 1.2 (n = 251) or 1.8 mg (n = 247), or oral glimepiride 8 mg (n = 248), each administered once daily in a double-blind fashion for 52 weeks (table IV).[9] Thereafter, patients who completed treatment were able to continue with open-label liraglutide for a further 52 weeks.[10]

Liraglutide monotherapy was an effective treatment for patients with early-stage type 2 diabetes in LEAD-3, providing clinically relevant improvements in glycaemic control parameters and stable glycaemic control over 52[9] weeks, which were sustained over the further 52-week open-label treatment period.[10] At the 52- and 104-week evaluations of the intention-to-treat (ITT) and completer populations, respectively,

Table IV. Summary of design details and endpoints in randomized, comparative trials of subcutaneous liraglutide, including the LEAD studies, in adult patients (pts) with type 2 diabetes mellitus. See table V, table VI and table VII for details of comparators and treatment regimens. Primary analyses were conducted on the intent-to-treat population, with hierarchical testing for noninferiority and superiority performed on glycaemic endpoint results in some studies

Study	Design	Duration (wk)	Antidiabetic treatment at baseline (mg/d)	Primary endpoint[a]	Main secondary endpoints[a,b]
Monotherapy					
LEAD-3[9,10]	db, dd, pc, ac, mc	52, 104	Lifestyle modification or monotherapy with an OAD[c]	HbA_{1c} at wk 52[d]	FPG, PPG, proportion of pts achieving HbA_{1c} <7% or ≤6.5%, HOMA-B, HOMA-IR, bodyweight, BP
Seino et al.,[24] Kaku et al.[72]	db, dd, ac, mc	24, 52	Lifestyle modification or monotherapy with an OAD[c]	HbA_{1c} at wk 24	FPG, PPG, proportion of pts achieving HbA_{1c} <7% or ≤6.5%, HOMA-B, bodyweight, lipids
Dual therapy					
LEAD-1[11]	db, dd, pc, ac, mc	26	GLI 2–4	HbA_{1c} at wk 26	FPG, PPG, proportion of pts achieving HbA_{1c} <7% or ≤6.5%, HOMA-B, HOMA-IR, bodyweight, BP
LEAD-2[12]	db, dd, pc, ac, mc, mn	26	MET 1500–2000	HbA_{1c} at wk 26	FPG, PPG, proportion of pts achieving HbA_{1c} <7% or ≤6.5%, HOMA-B, bodyweight, BP
Kaku et al.,[22] Seino et al.[71]	db, pc, mc	24, 52	SU[e]	HbA_{1c} at wk 24	FPG, PPG, proportion of pts achieving HbA_{1c} <7% or ≤6.5%, PPG, HOMA-B, bodyweight, lipids, BP
Pratley et al.[19,20]	nb, ac, mc, mn	26, 52	MET ≥1500	HbA_{1c} at wk 26[f]	FPG, PPG, proportion of pts achieving HbA_{1c} <7% or ≤6.5%, HOMA-B, HOMA-IR, bodyweight, lipids
Yang et al.[21]	db, dd, ac, mc	16	MET 2000	HbA_{1c} at wk 16	FPG, PPG, proportion of pts achieving HbA_{1c} <7% or ≤6.5%, HOMA-B, bodyweight, BP
Dual or triple therapy					
LEAD-6[13,70]	nb, ac, mc, mn	26, 40[g]	MET and/or SU	HbA_{1c} at wk 26	FPG, PPG, proportion of pts achieving HbA_{1c} <7% or ≤6.5%, bodyweight, lipids, BP
Triple therapy					
LEAD-4[15]	db, pc, ac, mc	26	MET 2000 + ROS 8	HbA_{1c} at wk 26	FPG, PPG, proportion of pts achieving HbA_{1c} <7% or ≤6.5%, HOMA-B, HOMA-IR, lipids, BP
LEAD-5[16]	db/nb, pc, ac, mc	26	MET 2000 + GLI 2–4	HbA_{1c} at wk 26	FPG, PPG, proportion of pts achieving HbA_{1c} <7% or ≤6.5%, bodyweight, BP

a Change from BL.

b See references for further details regarding secondary endpoints.

c Up to half of the maximum approved dose.

d Also assessed at wk 104 as a secondary endpoint.

e Monotherapy with one of three sulfonylurea drugs.

f Also assessed at wk 52.

g This includes a 14-wk nonrandomized extension of the 26-wk trial when pts switched from exenatide to liraglutide treatment.

ac = active comparator; **BL** = baseline; **BP** = blood pressure; **db** = double-blind; **dd** = double-dummy; **FPG** = fasting plasma glucose; **GLI** = oral glimepiride; **HbA_{1c}** = glycosylated haemoglobin; **HOMA-B** = homeostasis model assessment index of β-cell function; **HOMA-IR** = homeostasis model assessment index of insulin resistance; **mc** = multicentre; **MET** = metformin; **mn** = multinational; **nb** = nonblind; **OAD** = oral antidiabetic drug; **pc** = placebo-controlled; **PPG** = postprandial plasma glucose; **ROS** = oral rosiglitazone; **SU** = oral sulfonylurea.

both dosages of liraglutide were significantly more effective than glimepiride, based on primary endpoint assessments of changes from baseline in HbA_{1c}, as shown in figure 1.

In addition, a significantly larger proportion of liraglutide 1.2 or 1.8 mg than glimepiride recipients achieved the American Diabetes Association (ADA) target of HbA_{1c} <7% at both 52- and 104-week assessments: 43%, 51% and 28%, respectively, at week 52 ($p \leq 0.007$); 53%, 58% and 37%, respectively, at week 104 ($p \leq 0.03$).[9,10] FPG levels declined during the first 2 weeks' liraglutide treatment and by week 4 in the glimepiride group, and were stable thereafter. Compared with glimepiride recipients, patients treated with liraglutide 1.2 or 1.8 mg also had significantly greater reductions from baseline in FPG levels at 52 weeks, which were sustained over the 2-year treatment period. At week 52, changes from baseline in FPG levels in the liraglutide 1.2 mg, 1.8 mg and glimepiride groups were −0.84, −1.42 and −0.29, respectively ($p \leq 0.02$ for both dosages of liraglutide vs glimepiride);[9] corresponding changes at week 104 were −1.3, −1.5 and −0.3 ($p \leq 0.0015$ for both dosages of liraglutide vs glimepiride).[10] Changes from baseline in homeostasis model assessment index of β-cell function (HOMA-B) did not differ significantly between treatments, whereas homeostasis model assessment index of insulin resistance (HOMA-IR) decreased significantly from baseline with liraglutide but increased with glimepiride at week 52 ($p \leq 0.02$ vs glimepiride). After 2 years' treatment, increases in HOMA-B, fasting insulin and fasting C-peptide were reported in all treatment groups with no significant between-group difference; decreases in HOMA-IR were 1.1% and 0.8% for the liraglutide 1.2 mg and 1.8 mg groups compared with an increase of 0.8% for glimepiride ($p = 0.045$ for liraglutide 1.2 mg vs glimepiride).[10]

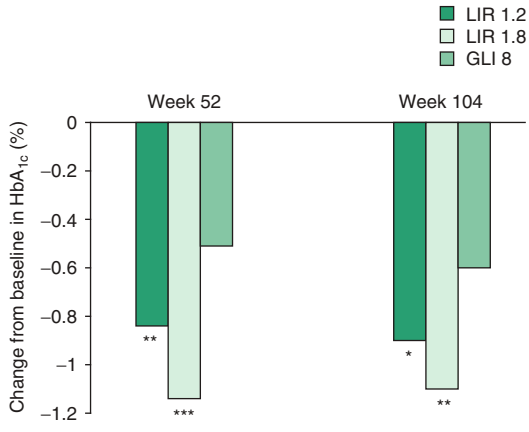

Fig. 1. Efficacy of liraglutide (LIR) 1.2 or 1.8 mg once daily compared with glimepiride (GLI) 8 mg once-daily monotherapy in patients with early-stage type 2 diabetes mellitus. Changes in mean glycosylated haemoglobin (HbA_{1c}) levels from baseline to weeks 52 and 104 in the LEAD-3 trial.[9,10] See table IV for study design details. At baseline, mean HbA_{1c} levels in the LIR 1.2 mg, 1.8 mg and GLI 8 mg once-daily treatment groups were 8.3%, 8.3% and 8.4%. * $p = 0.0376$; ** $p \leq 0.0016$; *** $p < 0.0001$ vs GLI.

Mean bodyweight also decreased significantly in patients who received liraglutide compared with recipients of glimepiride, who gained bodyweight, over the initial 52-week treatment period and this bodyweight loss was sustained over the subsequent 52-week open-label period.[9,10] At the week 104 assessment, changes in bodyweight in the liraglutide 1.2 mg and 1.8 mg groups were −2.1 kg and −2.7 kg compared with an increase of 1.1 kg in the glimepiride group ($p < 0.0001$).[10] SBP decreased from baseline by 2.1 and 3.6 mmHg ($p < 0.0118$ vs glimepiride) in the liraglutide 1.2 and 1.8 mg groups, respectively, compared with a decrease of 0.7 mmHg in the glimepiride treatment group at week 52; however, there were no significant between-group differences in SBP at the 104-week assessment.[9]

Consistent with the results of LEAD-3, which was conducted largely in a population of European descent, liraglutide monotherapy 0.9 mg once daily was an effective treatment for Japanese patients with type 2 diabetes, of whom ≈82% had received previous treatment with a single OAD.[24] In this randomized, double-blind 24-week trial (Seino et al.;[24] table IV) with a 28-week open-label extension,[72] reductions in HbA_{1c} levels were significantly greater with liraglutide 0.9 mg once daily (n = 268) [reduction from a mean level of 8.92% at baseline to 6.99% at week 24] than glibenclamide 1.25–2.5 mg once daily (n = 132) [reduction from 8.78% to 7.50%]. The difference in favour of liraglutide was −0.5% (95% CI −0.70, −0.30; $p < 0.0001$). Similarly, at week 24, patients in both treatment groups had significant reductions from

baseline in FPG levels (reduction from a mean level of 11.3 mmol/L at baseline to 7.6 mmol/L for liraglutide; reduction from 11.2 mmol/L to 8.3 mmol/L for glibenclamide). The difference in favour of liraglutide was –0.72 mmol/L (95% CI –1.0, –0.4; $p < 0.0001$). Furthermore, by week 24, patients treated with liraglutide had a mean reduction in bodyweight of 0.92 kg, whereas the glibenclamide recipients had a mean increase in bodyweight of 0.99 kg (between-group difference –1.91 kg; $p < 0.0001$).[24] At baseline, the mean bodyweight of liraglutide and glibenclamide recipients was 65.2 and 64.8 kg, respectively. At week 52, liraglutide also provided more favourable glycaemic control than glibenclamide;[72] at this timepoint, HbA_{1c} levels had decreased from 9.3% at baseline to 7.8% in the liraglutide group and from 9.2% at baseline to 8.2% in the glibenclamide group; treatment difference –0.49 (95% CI –0.71, –0.27). The Japanese Diabetes Society target HbA_{1c} of <6.9% was met by 22.1% of the liraglutide recipients and 8.5% of the glibenclamide recipients.[72]

4.2 Combination Therapy

4.2.1 In Combination with One Oral Antidiabetic Drug (OAD)

The efficacy of liraglutide as a second drug (i.e. as dual therapy) in patients with inadequate glycaemic control on pre-study OAD monotherapy has been evaluated in several studies of up to 26 weeks' in duration, including the LEAD-1[11] and -2[12] studies (table V). In LEAD-1 and -2, patients were receiving optimized/standardized background single-drug OAD therapy for 4–6 weeks before randomization.[11,12] After randomization, liraglutide dosages were titrated to 0.6, 1.2 or 1.8 mg once daily over a 2-week[11] or 2- to 3-week[12] period, and for the remaining 24 weeks patients remained on these dosages.

The addition of liraglutide as second-line treatment resulted in significantly greater reductions from baseline in HbA_{1c} levels than with placebo, i.e. glimepiride[11] or metformin monotherapy[12] in LEAD-1 and -2 at week 26 (table V). In addition, in LEAD-1, liraglutide 1.2 or 1.8 mg plus glimepiride produced significantly greater reductions from baseline in HbA_{1c} levels than rosiglitazone 4 mg/day plus glimepiride at week 26.[11] Liraglutide 1.2 or 1.8 mg in combination with metformin was noninferior to glimepiride plus metformin in LEAD-2 in reducing HbA_{1c} levels at week 26. Moreover, significantly more recipients of liraglutide 1.2 or 1.8 mg had achieved target HbA_{1c} levels by week 26. In terms of other secondary glycaemic control parameters, including FPG and PPG levels, liraglutide combination therapy was also significantly ($p < 0.05$) more effective than combination therapy with rosiglitazone, or glimepiride or metformin monotherapy. In general, changes in indices of pancreatic β-cell function also favoured liraglutide, with decreases in the proinsulin-to-insulin ratio in the liraglutide 1.8 mg treatment groups greater than those observed in the placebo monotherapy groups.[11,12,78] In addition, recipients of liraglutide 0.6, 1.2 or 1.8 mg had mean increases from baseline in HOMA-B ranging from 19% to 35% in LEAD-1 and from 23% to 28% in LEAD-2, compared with increases of 13% with rosiglitazone (LEAD-1) and 25% with glimepiride combination therapy and no change in the placebo group in LEAD-2.[11,12]

Liraglutide was also significantly more effective than the comparators in reducing bodyweight during the LEAD-1 and -2 studies (table V). Reductions from baseline in SBP ranging from 2 to 3 mmHg also occurred during treatment with liraglutide 1.2 and 1.8 mg in the LEAD-1 and -2 trials; recipients of rosiglitazone or placebo (glimepiride) had decreases in SBP ranging from 0.9 to 2.3 mmHg in LEAD-1, and recipients of glimepiride combination therapy had an increase in SBP of 0.4 mmHg ($p < 0.05$) in LEAD-2.[11,12]

Liraglutide was more effective than sitagliptin in terms of glycaemic control at both 26- and 52-week evaluation timepoints in a trial conducted across 11 European countries, the US and Canada[19,20] (table V). At week 26, the estimated mean treatment difference in HbA_{1c} in favour of liraglutide 1.8 mg versus sitagliptin was –0.60% (95% CI –0.77, –0.43; $p < 0.0001$) and for liraglutide 1.2 mg versus sitagliptin the difference was –0.34% (95% CI –0.51, –0.16; $p < 0.0001$), with similar results reported for the per-protocol population. The efficacy of liraglutide was sustained over a

Table V. Efficacy of liraglutide (LIR) in combination with one oral antidiabetic drug (OAD) [as dual therapy] in the treatment of adult patients (pts) with type 2 diabetes mellitus. Results of randomized, double-blind, active and/or placebo (PL)-controlled trials. Analyses were conducted on the intention-to-treat populations; hierarchical testing for noninferiority and superiority were undertaken in several studies

Study (duration in wk); co-administered OAD regimen mg/day	Treatment regimen (mg/day) [no. of pts]	Mean HbA_{1c} (%)		Mean FPG (mmol/L)		Pts at target HbA_{1c} (%)		Mean bodyweight (kg)	
		BL	change from BL[a]	BL	change from BL	<7%[b]	≤6.5%[c]	BL	change from BL
LEAD-1[11] (26); GLI 2–4	LIR 0.6 [233]	8.4	−0.6***	10.0	−0.72***	24***	13**	82.6	0.7††
	LIR 1.2 [228]	8.5	−1.1***††	9.8	−1.57***†	35***†	22***††	80.0	0.3††
	LIR 1.8 [234]	8.5	−1.1***††	9.7	−1.59***†	42***††	21***††	83.0	−0.2††
	ROS 4 [232]	8.4	−0.4***	9.9	−0.88	22	10	80.6	2.1
	PL [114]	8.4	0.2	9.5	1.01	8	4	81.9	−0.1
LEAD-2[12] (26); MET 1500–2000	LIR 0.6 [242]	8.4	−0.7***	10.2	−1.1***	28*	11*	NR	−1.8††
	LIR 1.2 [240]	8.3	−1.0***[d]	9.9	−1.6***	35*	20*	NR	−2.6**††
	LIR 1.8 [242]	8.4	−1.0***[d]	10.1	−1.7***	42*	25*	NR	−2.8**††
	GLI 4 [242]	8.4	−1.0***	10.0	−1.3	36	22	NR	1.0
	PL [121]	8.4	0.1	10.0	0.4	11	4	NR	−1.5
Kaku et al.[22] (24);	LIR 0.6 [88]	8.6	−1.46***[e]; −1.09[f]	9.86	−2.30***[e]	46.5***[e]	24.4***[e]	66.1	0.06[e]
Seino et al.[71] (52);	LIR 0.9 [88]	8.2	−1.56***[e]; −1.28[f]	9.18	−2.28***[e]	71.3***[e]	47.1***[e]	64.6	−0.37[e]
SU	PL [88]	8.45	−0.40[e]; −0.06[f]	9.48	−0.64[e]	14.8[e]	4.5[e]	66.7	−1.12[e]
Pratley et al.[19,20] (26,[19] 52[20]); MET ≥1500	LIR 1.2 [116]	8.4	−1.24††[g]; −1.29††[h]	10.1	−1.87††[g]; −1.71††[h]	44††[g]; 50.3††[h]	21††[g]; 24.3[h]	93.7	−2.86††[g]; −2.78††[h]
	LIR 1.8 [116]	8.4	−1.50††[g]; −1.51††[h]	9.9	−2.14††[g]; −2.04††[h]	54.6††[g]; 63.3††[h]	35.8††[g]; 40.4††[h]	94.6	−3.38††[g]; −3.68††[h]
	SIT 100 [120]	8.5	−0.90[g]; −0.88[h]	10.0	−0.83[g]; −0.59[h]	22[g]; 27.1[h]	11[g]; 16.8[h]	93.1	−0.96[g]; −1.16[h]
Yang et al.[21] (16); MET 2000	LIR 0.6 [231]	8.5	−1.14	9.8	NR	NR	NR	68.6	−1.80
	LIR 1.2 [233]	8.6	−1.36[i]	9.5	−2.05	42.9	26.2	67.4	−2.35
	LIR 1.8 [234]	8.6	−1.45[i]	9.9	−2.12	44.6	30.0	68.2	−2.44
	GLI 4 [231]	8.5	−1.39	9.6	−2.18	43.7	29.4	68.2	0.08

a Primary endpoint.

b American Diabetes Association guidelines.[75]

c American Association of Clinical Endocrinologists guidelines[76] and the International Diabetes Federation guidelines.[77]

d Noninferior to GLI (upper limit of two-sided 95% CIs for treatment difference was <0.4%, but not <0%, indicating superiority).

e Results at week 24.

f Baseline HbA_{1c} values for this dataset were 9.0% (LIR 0.6 mg), 8.61% (LIR 0.9 mg) and 8.85% (PL).[71]

g Results at wk 26.

h Results at wk 52.

i Noninferior to GLI, as the upper limit of the two-sided 95% CIs for the treatment difference was <0.4%.

BL = baseline; **FPG** = fasting plasma glucose; **GLI** = oral glimepiride; **HbA_{1c}** = glycosylated haemoglobin; **MET** = oral metformin; **NR** = not reported; **ROS** = oral rosiglitazone; **SIT** = oral sitagliptin; **SU** = oral sulfonylurea; * $p < 0.05$, ** $p \leq 0.01$, *** $p < 0.0001$ vs PL; † $p \leq 0.0015$, †† $p < 0.0001$ vs active comparator.

further 26-week extension of this trial; after a total of 52 weeks' treatment, liraglutide remained more effective than sitagliptin in reducing HbA_{1c} from baseline (table V).

Liraglutide reduced HbA_{1c} levels to a significantly ($p < 0.01$) greater extent than sitagliptin (at week 26) across a range of baseline HbA_{1c} levels (≤7.5% to >9.0% [excluding >8.5–9.0%]), in a *post hoc* analysis of the study reported as an abstract.[79] Reductions in HbA_{1c} levels were greater in patients with higher baseline levels, with reductions from baseline (7.5% to >9.0%) ranging from 0.9% to 2.3% for liraglutide and from 0.2% to 1.4% for sitagliptin recipients.[79]

At week 26, compared with sitagliptin, significant improvements in HOMA-B, C peptide and proinsulin-to-insulin ratio occurred in the liraglutide treatment groups but there were no between-group differences in HOMA-IR results.[19] Improvements in indicators of β-cell function were sustained during the subsequent 26-week treatment period and the greater reduction in HOMA-IR attained with liraglutide versus sitagliptin treatment was statistically significant ($p < 0.05$).[20] Patients treated with liraglutide had significantly greater reductions from baseline in mean total cholesterol levels than the sitagliptin treatment group: reductions of 0.03 and 0.17 mmol/L for liraglutide 1.2 and 1.8 mg, respectively, compared with a reduction of 0.02 mmol/L for sitagliptin; there were no other differences between the two treatments in lipid profiles at week 26.[19]

Administered in combination with metformin, liraglutide was noninferior to glimepiride in terms of glycaemic control over a 16-week treatment period in Asian patients from China, South Korea and India (table V).[21] The effects on glycaemic parameters observed in this population are similar to those reported in Caucasian, Hispanic and African American populations in global phase III trials of liraglutide.[21] Furthermore, in Japanese patients with type 2 diabetes, the addition of liraglutide to a sulfonylurea led to dose-dependent improvements in glycaemic control compared with sulfonylurea monotherapy over a 24-week treatment period (table V)[22] and during a subsequent 28-week extension.[71] At week 52, compared with placebo, the mean differences in HbA_{1c} levels for the liraglutide 0.6 and 0.9 mg treatment groups were, respectively, 0.96 (95% CI −1.25, −0.67) and −1.33 (95% CI −1.62, −1.04). The Japanese Diabetes Society target HbA1c of <6.9% was met by 15.1%, 39.1% and 4.5% of patients in the liraglutide 0.6 mg, 0.9 mg and placebo groups, respectively, at this timepoint.[71]

4.2.2 In Combination with One or Two OADs

In adults with type 2 diabetes inadequately controlled by maximally tolerated dosages of a sulfonylurea or metformin or both in combination, when added to ongoing OAD treatment, liraglutide provided significantly better glycaemic control than exenatide in the LEAD-6 study (table VI).[13] Recipients of liraglutide had significantly greater decreases in HbA_{1c} levels than the patients treated with exenatide, and a significantly larger proportion of liraglutide than exenatide recipients achieved the target HbA_{1c} levels at week 26 (table VI). Significant improvements, in favour of liraglutide, in FPG (table VI) and HOMA-B (32.1% vs 2.7%; $p < 0.0001$) were also observed at week 26, with reductions in bodyweight being similar for the two treatment groups (table VI).[13]

In a 14-week extension of this study designed to evaluate the clinical profile of liraglutide in patients switching from previous exenatide treatment, liraglutide provided further improvements in glycaemic control.[70] At the end of the extension phase, compared with week 26, patients who switched from exenatide to liraglutide had significant reductions in HbA_{1c} levels and experienced significant improvements over the 14-week period in other parameters, including FPG and bodyweight (table VI). Consistent with the reduction in FPG levels, there was a significant increase in HOMA-B of 14.5 ± 4.4% in the switch group. In the patients who continued to receive liraglutide during the extension period, there was a further reduction (not statistically significant) in FPG levels, bodyweight (table VI) and SBP (−2.2 ± 0.88 mmHg; $p = 0.0128$). At the end of the extension period, there were no significant changes in either group in other parameters, including fasting insulin, proinsulin-to-insulin ratio or HOMA-IR. The only significant change in PPG was in the group that switched to liraglutide, with

Table VI. Efficacy of subcutaneous liraglutide (LIR) compared with subcutaneous exenatide (EXE) each in combination with one or two oral antidiabetic drugs (OADs) in the treatment of adult patients (pts) with type 2 diabetes mellitus inadequately controlled on previous OAD therapy. Results of a randomized, open-label, multicentre trial in pts receiving ongoing oral treatment with metformin (MET) and/or a sulfonylurea (SU)[13] and results of an extension phase of this trial in which pts previously treated with EXE switched to LIR.[70] Analyses were conducted on the intention-to-treat population; hierarchical testing for noninferiority and superiority were also undertaken

Study (duration in wk); co-administered OAD regimen mg/day	Treatment regimen (mg/day) [no. of pts]	Mean HbA_{1c} (%)		Mean FPG (mmol/L)		Pts at target HbA_{1c} (%)		Mean bodyweight (kg)	
		BL	change from BL[a]	BL	change from BL	<7%[b]	≤6.5%[c]	BL	change from BL
LEAD-6[13] (26)	LIR 1.8 [233]	8.2	–1.12**	9.8	–1.61**	54*	35**	93.1	–3.24
MET and/or SU	EXE 20 μg[d] [231]	8.1	–0.79	9.5	–0.60	43	21	93.0	–2.87
LEAD-6 [70]	LIR 1.8 [202]	7.0	–0.06	7.7	–0.2	NR	NR	91.0	–0.4
(14 wk extension)	LIR 1.8 [187][e]	7.2	–0.32†	8.6	–0.9†	NR	NR	91.0	–0.9†

a Primary endpoint.

b American Diabetes Association guidelines.[75]

c American Association of Clinical Endocrinologists guidelines[76] and the International Diabetes Federation guidelines.[77]

d Administered as 10 μg twice daily.

e Patients switched from EXE treatment at wk 26.

BL = baseline; **FPG** = fasting plasma glucose; **HbA_{1c}** = glycosylated haemoglobin; * $p = 0.0015$, ** $p < 0.0001$ vs EXE; † $p < 0.0001$ vs values at wk 26.

one PPG measurement taken after lunch attaining statistical significance (–0.64 ± 0.21 mmol/L; $p = 0.0032$).[70]

4.2.3 In Combination with Two OADs

The LEAD-4 and -5 studies were conducted to compare the efficacy of liraglutide with that of placebo (i.e. two OADs)[15,16] and insulin glargine[16] in patients receiving ongoing treatment with metformin and rosiglitazone or glimepiride (table VII) [i.e. as triple therapy]. In both studies, liraglutide plus two OADs was significantly more effective than placebo (i.e. two OADs) in reducing HbA_{1c} levels (reductions in HbA_{1c} levels ranged from 1.3% to 1.5% across the liraglutide groups), with significantly larger proportions of liraglutide than comparator recipients achieving target HbA_{1c} levels at week 26 (table VII). In addition, in LEAD-4, decreases from baseline in the proinsulin-to-insulin ratio occurred in both liraglutide groups compared with an increase in the placebo group ($p < 0.05$ for both liraglutide treatment groups vs placebo). The increase in HOMA-B reported in patients treated with liraglutide 1.8 mg or 1.2 mg in LEAD-4 was significantly greater than that observed with placebo (27% for each of the liraglutide groups vs 6% of placebo; $p < 0.0001$).[15] Insulin resistance, measured by HOMA-IR, decreased in the liraglutide and placebo groups and there were no significant between-groups differences.[15]

Reductions from baseline in mean bodyweight, which ranged from –1.0 to –2.0 kg in the liraglutide groups, were also significantly greater with liraglutide 1.2 and 1.8 mg than with placebo or insulin glargine. Indeed, recipients of insulin glargine gained weight in LEAD-5, as did placebo recipients in LEAD-4 (table VII). Patients treated with liraglutide also had reductions in SBP that achieved significance compared with placebo in LEAD-4 (placebo-corrected differences were –5.6 and –4.5 mmHg for liraglutide 1.2 and 1.8 mg, respectively; $p \leq 0.0009$).[15] In LEAD-5, patients treated with liraglutide 1.8 mg once daily had a reduction in SBP of 4.0 mmHg, whereas patients who received insulin glargine had an increase in SBP of 0.54 mmHg ($p = 0.0001$ for the between-group difference).[16] Liraglutide also produced beneficial changes in some lipid parameters in LEAD-4. Compared with placebo, patients treated with liraglutide 1.2 mg had significantly ($p < 0.05$) greater decreases from baseline in low-density lipoprotein cholesterol (–0.28 vs –0.10 mmol/L) and triglycerides (–0.38 vs –0.13 mmol/L).[15]

4.3 Patient-Reported Outcomes

Two studies have evaluated patient-reported outcomes and treatment satisfaction in patients with type 2 diabetes treated with liraglutide, glimepiride[80] (based on LEAD-2[12]) or sitagliptin,[19,81] each in combination with metformin, or metformin alone.[80,81] Patient-reported outcomes were also assessed in the LEAD-3 trial[9,82] and treatment satisfaction was evaluated in LEAD-6.[13] To assess patient outcomes, both studies used the Diabetes Treatment Satisfaction Questionnaire (DTSQ), which consists of two versions: a status version (DTSQs) and a change version (DTSQc).[80,81]

In the study that compared liraglutide with sitagliptin, assessments of treatment satisfaction using the DTSQs were conducted at baseline and at week 26, or when treatment was withdrawn, in a subgroup of patients (77% of patients exposed to study medication) for whom patient outcomes data were obtained.[81] The DTSQs comprised eight items, which were each analysed separately, whereas overall treatment satisfaction was calculated by adding scores for six items: current treatment, convenience, flexibility, understanding, recommend, continue. Scores were on a scale ranging from 0 (very dissatisfied/inconvenient) to 6 (very satisfied/convenient). Frequency of hypoglycaemia and hyperglycaemia, as perceived by the patient, were measured separately and scores from 0 (none of the time, i.e. perceived low frequency) to 6 (most of the time, i.e. perceived high frequency).[81]

Scores at baseline indicated similar levels of treatment satisfaction for the three treatment groups, and treatment satisfaction scores improved in all treatment groups by week 26. Overall treatment satisfaction at week 26 was, however, significantly ($p = 0.03$) greater in the liraglutide 1.8 mg than in the sitagliptin groups (significant improvements in 'current treatment', 'recommend' and 'continue'), whereas differences between the two liraglutide groups and between liraglutide 1.2 mg and sitagliptin did not attain statistical significance.[81] In addition, hyperglycaemia was perceived significantly less often with liraglutide 1.8 and 1.2 mg than with sitagliptin ($p \leq 0.01$); there were no between-group differences in the perceived frequency of hypoglycaemia.[81]

Patients' satisfaction with all dosages of liraglutide (plus metformin) treatment was scored significantly ($p < 0.05$) higher on DTSQc than with metformin monotherapy and was similar to that with glimepiride plus metformin in the study that included a subpopulation of patients from LEAD-2.[80] At week 26, recipients of liraglutide perceived a significantly ($p < 0.05$) lower incidence of hyperglycaemia than did metformin recipients and a significantly ($p < 0.05$) lower incidence of

Table VII. Efficacy of subcutaneous liraglutide (LIR) in combination with two oral antidiabetic drugs (OADs) [as triple therapy] in the treatment of adult patients (pts) with type 2 diabetes mellitus. Results of randomized, double-blind, active and/or placebo (PL)-controlled trials. Analyses were conducted on the intention-to-treat populations; hierarchical testing for noninferiority and superiority were undertaken

Study (duration in wk); co-administered OADs mg/day	Treatment regimen (mg/day) [no. of pts]	Mean HbA_{1c} (%)		Mean FPG (mmol/L)		Pts at target HbA_{1c} (%)		Mean bodyweight (kg)	
		BL	change from BL[a]	BL	change from BL	<7%[b]	≤6.5%[c]	BL	change from BL
LEAD-4 [15] (26);	LIR 1.2 [178]	8.5	−1.5*	10.1	−2.2*	58*	37*	95.5	−1.0*
MET 2000 +	LIR 1.8 [178]	8.6	−1.5*	10.3	−2.4*	54*	36*	94.9	−2.0*
ROS 8	PL [177]	8.4	−0.5	10.0	−0.4	28	14	98.3	0.6
LEAD-5[16] (26);	LIR 1.8 [232]	8.3	−1.3*††	9.1	−1.55*	53*†	37*†††	85.5	−1.81*†††
MET 2000 +	INS [234]	8.2	−1.1	9.1	−1.7	46	24	85.0	1.62
GLI 2–4	PL [115]	8.3	−0.2	9.4	0.53	16	11	85.7	−0.42

a Primary endpoint.

b American Diabetes Association guidelines.[75]

c American Association of Clinical Endocrinologists guidelines[76] and the International Diabetes Federation guidelines.[77]

BL = baseline; **FPG** = fasting blood glucose; **HbA_{1c}** = glycosylated haemoglobin; **INS** = insulin glargine; **PL** = placebo; * $p < 0.0001$ vs PL; † $p = 0.01$, †† $p = 0.0015$, ††† $p < 0.0001$ vs INS.

hypoglycaemia compared with that perceived by patients who received glimepiride plus metformin.[80]

Results of another patient-reported outcomes study, conducted as part of LEAD-3[9] (section 4.1), showed that improvements in glycaemic control and decreases in bodyweight achieved with liraglutide versus glimepiride monotherapy may result in patients with type 2 diabetes having improvements in psychological and emotional well-being and better health perceptions.[82] The study used a validated type 2 diabetes self-administered assessment questionnaire consisting of 77 questions as part of a battery of scales (including body image, bodyweight perception and quality-of-life scales). All patients completed the questionnaire at baseline (week 0), at week 28 and at week 52 (the end of the double-blind phase of the study). Patient assessments of bodyweight were significantly ($p = 0.002$) more favourable for liraglutide 1.8 mg/day than for glimepiride 8 mg/day recipients, and patients treated with liraglutide 1.8 mg were 52% less likely to feel overweight. Other assessments that significantly favoured liraglutide versus glimepiride included concern about bodyweight (liraglutide 1.2 mg and 1.8 mg; $p < 0.001$), mental and emotional health ($p = 0.012$) and general perceived health ($p = 0.033$). There were no reports of favourable outcomes for glimepiride compared with liraglutide.[82]

In LEAD-6 (section 4.2), overall treatment satisfaction was rated higher by liraglutide-treated patients ($n = 161$) than by 143 exenatide recipients. The DTSQ was used with treatment satisfaction assessed on 6 of 8 items (each scored from +3 [better] to −3 [worse]): treatment scores for the liraglutide and exenatide groups were 15.18 vs 13.30; $p = 0.0004$.[13]

5. Tolerability

5.1 General Profile

Liraglutide, administered subcutaneously once daily at various dosages as monotherapy[9,10,24,72] or in combination with one or two OADs,[11-13,15,16,19-22,70,71] was generally well tolerated over treatment periods of up to 104 weeks by adults with type 2 diabetes in randomized controlled trials or open-label extensions. Most reported adverse events in recipients of liraglutide were gastrointestinal (most commonly nausea and diarrhoea), which were mild or moderate in nature and tended to resolve after the first few weeks of treatment. Statistical analyses were generally not reported.[9-13,15,16,19-21,70] Injection-site reaction (e.g. erythema, injection site rash), usually mild and not leading to treatment discontinuation, occurred in approximately 2% of recipients of liraglutide in controlled trials of at least 26 weeks' duration.[7,8] Serious adverse events were seldom reported across all of the clinical trials. Over the 2-year period of treatment with liraglutide as monotherapy in LEAD-3, gastrointestinal adverse events were reported in 54% and 53% of liraglutide 1.2 mg and 1.8 mg recipients, respectively, compared with 28% of patients treated with glimepiride; corresponding rates of nausea were 29%, 31% and 9%.[10] There was no notable change in the tolerability profile of liraglutide over time in the LEAD-3 trial and none of the liraglutide recipients discontinued treatment because of nausea during the 52-week extension.[10]

Adverse events (pooled data) reported in ≥5% of liraglutide recipients and occurring more frequently with liraglutide than with placebo in 26-week trials of liraglutide in combination with one or two OADs are shown in figure 2 (LEAD-1 and -2) and figure 3 (LEAD-4 and -5).

Across these four trials nausea was reported in 7.5–34.6% and diarrhoea in 7.2–14.1% of patients who received liraglutide. In LEAD-2, -4 and -5 (but not in LEAD-1), vomiting occurred at an incidence >5% and more frequently with liraglutide (6.5–12.4%) than with placebo (i.e. OAD monotherapy or dual therapy), as did headache (8.2–9.6%).

Treatment-emergent gastrointestinal events occurred more frequently with liraglutide 1.2 mg (incidence 33%) and 1.8 mg (40%) than with sitagliptin (21%) over 26 weeks in the randomized comparative trial.[19] However, there were no marked between-group differences in the incidence of other treatment-related adverse events occurring at an incidence of ≥12%.[19] Over 52 weeks, ≤6% of patients treated with liraglutide 1.2 or 1.8 mg experienced serious adverse events, compared

with 5.5% of sitagliptin recipients. Three deaths occurred during this time, but none were considered to be related to the study drug.[20] In LEAD-6, there was a similar distribution and incidence of adverse events in the liraglutide 1.8 mg and exenatide 10 μg twice-daily treatment groups over the 26-week treatment period, with treatment-related gastrointestinal disorders reported in 45.5% and 42.7% of liraglutide and exenatide recipients, respectively.[13] However, although nausea was reported by similar proportions of patients in each group initially, nausea persisted for longer in the exenatide-treated patients, occurring in 5 (3%) of 202 liraglutide and in 16 (9%) of 186 exenatide recipients at week 26.[13] During the 14-week subsequent open-label extension to this trial,[70] nausea was reported in more than twice as many patients who switched from exenatide to liraglutide than in those who continued liraglutide treatment (3.2% vs 1.5%), whereas corresponding rates of vomiting were 0.5% vs 2.0%. [70] The tolerability of liraglutide was not adversely affected in type 2 diabetic patients with mild renal impairment in a meta-analysis of data from the six LEAD trials.[55]

Drugs containing peptides or proteins, such as liraglutide, potentially have immunogenic properties and may elicit the formation of antibodies to the drug (section 2).[7,8] In randomized controlled trials of at least 26 weeks' duration, low titres of anti-liraglutide antibodies were detected in an average of 8.6% of patients treated with liraglutide but were not associated with a reduction in efficacy of the drug. The most common category of adverse event in the patients with anti-liraglutide antibodies was infection (primarily nonserious upper respiratory tract infection), which was reported in 40% of patients with anti-liraglutide antibodies; by comparison, infection was reported in, respectively, 36%, 34% and 35% of recipients of liraglutide who were liraglutide antibody-negative, placebo recipients or patients treated with an active control. The presence of anti-liraglutide antibodies was not associated with a decrease in the efficacy of liraglutide in terms of reductions in mean HbA_{1c} levels, although three patients with the highest titers of anti-liraglutide antibodies did not have a reduction from baseline in HbA_{1c} levels during treatment with liraglutide.[8]

GLP-1 analogues have been associated with a risk of pancreatitis.[7] In clinical trials, there were more cases of pancreatitis in patients treated with liraglutide than in recipients of the comparator drugs, although there have been few reported acute pancreatitis events overall.[7,8] The number of cases of acute pancreatitis seen during the LEAD trials is lower than the incidence reported in previous studies of patients with type 2 diabetes.[83-86] Although liraglutide has not shown nephrotoxicity in animal studies or clinical trials, there are postmarketing reports of acute renal failure and worsening of chronic renal failure.[8] There is a boxed warning in the US prescribing information[8] stating that liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumours at clinically relevant exposures

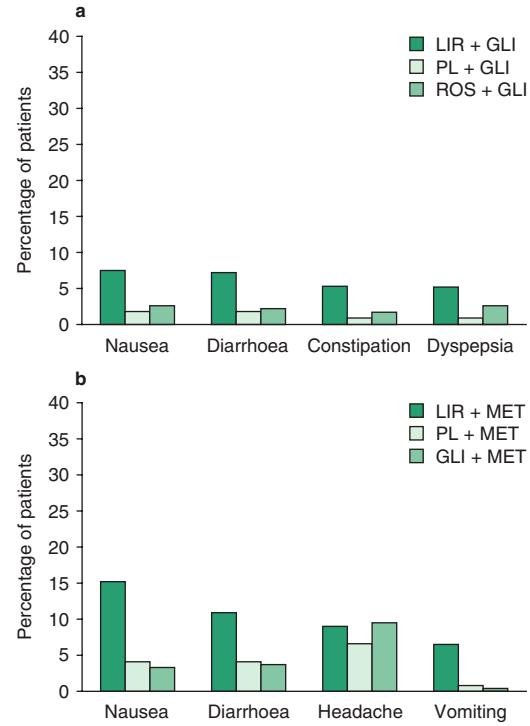

Fig. 2. Tolerability profile of subcutaneously administered liraglutide (LIR) and comparators (each in combination with an oral antidiabetic drug) in adults with type 2 diabetes mellitus in the (**a**) LEAD-1 and (**b**) LEAD-2 trials.[8] Adverse events reported in ≥5% of LIR recipients and occurring more frequently than with placebo (PL) over a 26-week treatment period. See section 4 for details of treatment regimens. **GLI** = glimepiride; **MET** = metformin; **ROS** = rosiglitazone.

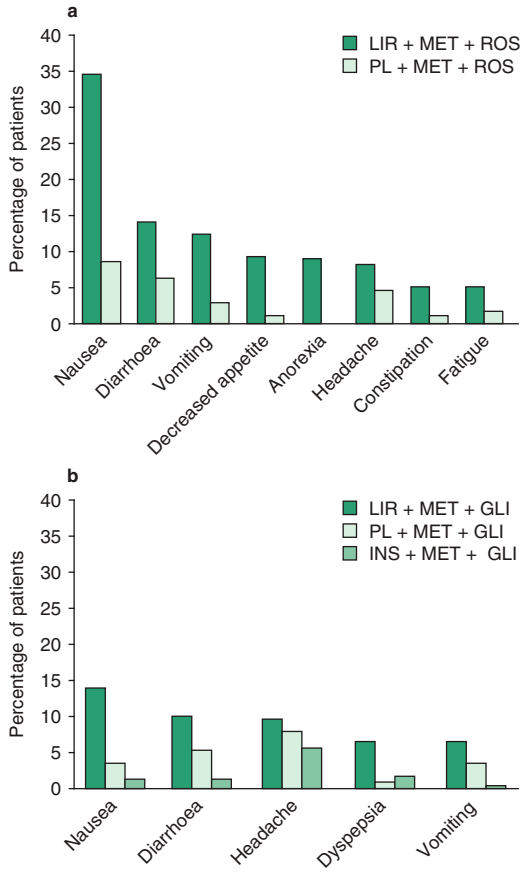

Fig. 3. Tolerability profile of subcutaneously administered liraglutide (LIR) and comparators (each in combination with two oral antidiabetic drugs) in adults with type 2 diabetes mellitus in the (**a**) LEAD-4 and (**b**) LEAD-5 trials. Adverse events reported in ≥5% of LIR recipients and occurring more frequently than with placebo (PL) over a 26-week treatment period. See section 4 for details of treatment regimens.[8] **GLI** = glimepiride; **INS** = insulin glargine; **MET** = metformin; **ROS** = rosiglitazone.

in both genders of rats and mice (section 2). Whether liraglutide causes thyroid C-cell tumours, including MTC in humans, is as yet unknown. Thus, liraglutide is contraindicated in patients with a personal or family history of MTC and in patients with multiple endocrine neoplasia syndrome type 2. Although monitoring with serum calcitonin or thyroid ultrasound was conducted during clinical trials, this may have increased the number of unnecessary thyroid surgeries. It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate the risk of thyroid C-cell tumours in humans. Patients receiving treatment with liraglutide should therefore be counselled regarding the risk and symptoms of thyroid tumours.[8]

5.2 Hypoglycaemia

In the clinical trials of subcutaneous liraglutide in adults with type 2 diabetes reviewed in section 4, hypoglycaemia was generally defined as a plasma glucose level of <3.1 mmol/L, with self-treated episodes regarded as minor and episodes requiring medical intervention or third-party assistance considered major. In these trials, the incidence of major or minor episodes of hypoglycaemia in recipients of liraglutide was generally low; data pertaining to minor or major episodes of hypoglycaemia are summarized in table VIII.

6. Pharmacoeconomic Considerations

Several cost-effectiveness/cost-utility analyses of liraglutide in adults with type 2 diabetes have been reported; two of these studies are fully published and were conducted from the US payer perspective.[87,88] A summary of the two US cost-effectiveness studies, the main focus of this section, is presented in table IX.

The cost-effectiveness analyses of liraglutide in adults with type 2 diabetes were well designed, with relevant costs included and sources of data clearly described in the fully published US studies.[87,88] In addition, clinical outcomes used in the models were relevant, appropriate discounting was used and sensitivity analyses were performed.

The objective of both US studies was the estimation of the cost effectiveness of subcutaneous liraglutide 1.2 mg[87] or 1.8 mg[87,88] once daily compared with that of a comparator, i.e. oral rosiglitazone 4 mg once daily[87] or exenatide 10 μg twice daily,[88] in adults with type 2 diabetes receiving ongoing OAD treatment. Clinical data and treatment effect assumptions were obtained from reports of the LEAD-1[11] and LEAD-6[13] trials (section 4). In both studies, the Center for Outcomes Research (CORE) Diabetes Model (CDM), a validated analysis tool that can be used to assess specific treatments for diabetes, was used

for the projection and comparison of 35-year clinical and economic outcomes, which included life expectancy, quality-adjusted life-years (QALYs), total costs and incremental cost-effectiveness ratios (ICERs). The 35-year time horizon was used to capture all relevant information relating to long-term diabetes complications and death in a population of type 2 diabetes patients with a mean age of 56 years at baseline. Sensitivity analyses included modification of the discount rate from 3% to 0% or 6%, adjustment of the time horizon from 35 years to 20 or 10 years and variation of liraglutide efficacy (using the upper and lower limits of the 95% CIs for HbA_{1c} changes from baseline with treatment).[87,88] Exclusion of the disutilities associated with body mass index,[87,88] or nausea[88] and an increased risk of congestive heart failure with rosiglitazone[87] were also included in the sensitivity analyses. Analyses of cost effectiveness were conducted using nonparametric bootstrapping to generate costs and clinical outcomes for 1000 hypothetical patients, each transitioning through the model 1000 times. Statistical analyses were not reported.

Liraglutide, administered as add-on therapy in combination with one or two OADs, appeared to be a cost-effective treatment for improving glycaemic control in patients with type 2 diabetes over a 35-year time horizon, assuming a $US50 000 per QALY cost-effectiveness threshold,[87,88] although liraglutide 1.8 mg did not quite meet this stringent definition in one of the studies.[87] Base-case ICERs for liraglutide 1.2 mg and 1.8 mg are shown in table IX.[87,88] Although the costs of 35 years of treatment with liraglutide 1.2 mg ($US46 836) and 1.8 mg $US67 553 were markedly higher than that of rosiglitazone ($US21 376), these costs were offset by improvements in quality-adjusted life expectancy and life expectancy in the liraglutide treatment groups. The costs of diabetes-related complications were similar (≈$US50 000) for the three treatment groups, with cardiovascular complications representing about 80% of these costs.[87] When compared with exenatide, differences in favour of liraglutide were attributed to between-group differences in HbA_{1c}, hypoglycaemic events and triglyceride levels. Over the projected 35-year treatment period, costs of treatment with liraglutide 1.8 mg and exenatide were $US64 067 and $US48 567, respectively, and corresponding complication costs were $US49 784 and $US52 429.[88] Overall, in both of the US studies, sensitivity analyses indicated that the findings were generally robust to a range of assumptions (table IX). Liraglutide was associated with benefits compared with exenatide in terms of life expectancy, reduced complication rates and QALYs in a long-term cost-effectiveness study that used clinical trial data from patients in six European countries (Denmark, Norway, Finland, Switzerland, the Netherlands and Austria).[89] Liraglutide was a cost-effective treatment from the perspective of the healthcare payer.[89]

Similarly, in economic evaluations of liraglutide (reported as abstracts), conducted from the perspective of the German or Bulgarian healthcare payer, which integrated clinical data from LEAD-1 and LEAD-6 trials with the CDM, liraglutide in addition to standard OAD treatment was a cost-effective treatment compared with rosiglitazone[90] or exenatide.[90,91] Liraglutide was also more cost effective than sitagliptin from the perspective of the German statutory health insurance system.[92]

Results of two US cost analyses of liraglutide monotherapy or combination therapy versus clinically relevant comparators (rosiglitazone plus glimepiride or glimepiride monotherapy) favoured liraglutide, although statistical analyses were not reported.[93,94]

Based on results from LEAD-2, patients were more willing to pay an extra $US3.63 per day for liraglutide than glimepiride, largely because of the beneficial effects of liraglutide on bodyweight compared with glimepiride.[95] Indeed, for a reduction in bodyweight of 2.6 kg with liraglutide, compared with an increase of 1 kg with glimepiride, patients were willing to pay $US3.48 per day. In addition, patients were willing to pay an extra $US0.70 per day for liraglutide to reduce SBP and $0.56 per day to decrease the risk of hypoglycaemic events.

7. Dosage and Administration

Liraglutide is indicated as an adjunct to diet and exercise to improve[8] or achieve[7] glycaemic control in adult patients with type 2 diabetes. It is available

Table VIII. Tolerability of liraglutide (LIR) in adult patients (pts) with type 2 diabetes mellitus. Incidence of minor hypoglycaemia and number of episodes of major hypoglycaemia in randomized controlled trials. Hypoglycaemia was generally defined as a plasma glucose level of <3.1 mmol/L, with self-treated episodes regarded as minor and episodes requiring medical intervention or third-party assistance considered major. Study drugs were administered once daily unless otherwise indicated; LIR and exenatide (EXE) were administered subcutaneously and all other agents were administered orally

Study	Incidence of minor hypoglycaemia	No. of episodes of major hypoglycaemia with LIR[a]
Monotherapy		
LEAD-3[9,10]	Significantly ($p < 0.0001$) lower rates of minor hypoglycaemia in both LIR 1.2 mg and 1.8 mg groups (not dose dependent) compared with the GLI 8 mg group: 0.30 and 0.25 vs 1.96 events per pt-year, at week 52.[9] Corresponding rates after 2 years' continuous therapy were 0.21 and 0.22 vs 1.75 ($p < 0.0001$ for both LIR comparisons vs GLI)[10]	0[b]
Seino et al.[24]	Significantly lower rate of minor hypoglycaemic episodes with LIR 0.9 than with glibenclamide 1.25–5 mg (0.25 vs 1.58 events per pt-year; $p < 0.0001$)	0
Dual therapy		
LEAD-1[11]	Higher incidence with LIR 1.2 or 1.8 mg than with PL (0.51 and 0.47 vs 0.17 events per pt-year; $p = 0.048$ for comparison with LIR 1.2 mg) and than with ROS 4 mg (0.12 events per pt-year; $p = 0.0024$ and $p = 0.0065$ for comparisons with LIR 1.2 and 1.8 mg) at week 26	1[c]
LEAD-2[12]	No significant difference between LIR 0.6–1.8 mg and PL; significantly lower incidence with LIR 0.6–1.8 mg than with GLI 4 mg (0.03–0.14 vs 1.23 events per pt-year; $p < 0.001$), at week 26	0
Kaku et al.[22]	Incidence in the LIR 0.6 mg, LIR 0.9 mg and PL groups: 2.17, 1.96 and 1.01 events per pt-year, respectively	0
Pratley et al.[19,20]	Similar proportions of recipients of LIR 1.2 mg, LIR 1.8 mg or SIT 100 mg experienced minor hypoglycaemia at weeks 26 and 52: ≈5% of pts at week 26 (0.178. 0.161[d] and 0.106 episodes per pt-year); 0.143, 0.154[d] and 0.137 episodes per pt-year, respectively, at week 52	1[e]
Yang et al.[21]	Lower incidence of episodes with LIR 0.6, 1.2 and 1.8 (2.6%, 0% and 1.7%) than with GLI 4 mg (19.0%) [statistical significance not reported] at week 16	0[f]
Dual or triple therapy		
LEAD-6[13,70]	Significantly fewer minor episodes in LIR 1.8 than EXE 20 μg recipients (1.9 vs 2.6 events per pt-year; $p = 0.0131$) at week 26. At week 40, in pts switched from EXE to LIR, there were 1.3 (reduced from 2.6) compared with 0.74 events per pt-year in pts treated with LIR for 40 weeks	1[g]
Triple therapy		
LEAD-4[15]	At week 26, LIR 1.8 mg recipients had a higher incidence of minor hypoglycaemia compared with PL (0.6 vs 0.2 events per pt-year; $p = 0.004$)	0
LEAD-5[16]	At week 26, similar incidence with LIR 1.8 and INS (1.2 vs 1.3 events per patient-year); 1.0 event per pt-year for PL	5[h]

a Actual incidence not reported.

b No episodes of major hypoglycaemia during the actual study, but one episode in recipients of LIR 1.8 mg after insulin infusion as part of a substudy procedure.

c One pt receiving LIR 1.8 mg plus GLI.

d Excluding one outlier.

e One report of major hypoglycaemia in a recipient of LIR 1.2 mg + MET during the first 26 weeks of treatment.

f No episodes in the LIR treatment groups over 16 weeks; two recipients of GLI had major hypoglycaemia.

g No episodes of major hypoglycaemia with LIR over 26 weeks; two exenatide recipients had major hypoglycaemic episodes; one pt continuing LIR had a major episode during the extension.

h Five pts receiving LIR 1.8 mg plus GLI plus MET.

GLI = glimepiride; **INS** = insulin glargine; **MET** = metformin; **PL** = placebo; **pt** = patient; **ROS** = rosiglitazone; **SIT** = sitagliptin.

as a solution containing liraglutide 6 mg/mL for injection in a pre-filled pen containing 18 mg in 3 mL that delivers doses of 0.6 mg, 1.2 mg or 1.8 mg.[7,8]

Liraglutide is not recommended as first-line therapy for patients who have inadequate glycaemic control on diet and exercise.[8] In patients

Table IX. Summary of cost-effectiveness/cost-utility analyses of liraglutide (LIR) administered subcutaneously once daily in adults with type 2 diabetes mellitus. Patients were also receiving oral therapy with either glimepiride (GLI),[87] metformin (MET) or GLI or GLI plus MET.[88] The annual rate of discounting for costs and outcomes was 3% in both studies

Study (country, y of costing)	Study perspective	Time horizon	Treatment regimen	Life expectancy, mean (y)	Total lifetime costs ($US)	QALY gained	Incremental cost/QALY gained (ICER) [$US]	
							base case	sensitivity analysis
Lee et al.[87] (US, 2008)	Healthcare payer[a]	35 y	LIR 1.2 mg od	13.335	107 300	8.828	34 147 vs ROS	Results in both LIR groups sensitive to changes in the time
			LIR 1.8 mg od	13.408	128 247	8.901	56 190 vs ROS	horizon (10 y) and downward adjustment of the HbA_{1c}
			ROS 4 mg od	12.367	81 205	8.064		assumption (to the lower boundary of the 95% CI), and increased CHF risk in the ROS group
Lee et al.[88] (US, 2010)	Healthcare payer[b]	35 y	LIR 1.8 mg od	12.829	125 287	8.458	40 282	Results sensitive to changes in the time horizon (10 y) and
			EXE 10 μg bid	12.642	112 331	8.137		downward adjustment of the HbA_{1c} assumption (to the lower boundary of the 95% CI)

a US private payer healthcare system.

b US healthcare system.

bid = twice daily; **CHF** = congestive heart failure; **EXE** = subcutaneous exenatide; **HbA_{1c}** = glycosylated haemoglobin; **ICER** = incremental cost-effectiveness ratio; **od** = once daily; **QALY** = quality-adjusted life-year; **ROS** = rosiglitazone.

with insufficient glycaemic control despite receiving the maximum tolerated dose of metformin or sulfonylurea monotherapy, liraglutide may be added and administered in combination with metformin or a sulfonylurea.[7] In patients with insufficient glycaemic control despite dual therapy, liraglutide may be administered in combination with metformin and a sulfonylurea or metformin and a thiazolidinedione.[7] Liraglutide is administered by subcutaneous injection in the abdomen, thigh or upper arm once daily at any time, without regard to meals.[7,8] Although the injection site and time of administration can be changed without dose adjustment, it is preferable that liraglutide is injected at about the same time of day.[7]

The starting dose of liraglutide is 0.6 mg once daily.[7,8] This low dose is intended to reduce the incidence of gastrointestinal symptoms and is not effective for glycaemic control.[8] After 1 week[8] or at least 1 week,[7] the dose of liraglutide should be increased to 1.2 mg once daily.[7,8] Thereafter, depending on clinical response, after at least 1 week,[7] some patients may benefit from a further increase in dose to 1.8 mg to further improve glycaemic control.[7,8] Daily doses higher than 1.8 mg are not recommended. If liraglutide is added to an existing regimen of metformin alone or in combination with a thiazolidinedione, dosages of these drugs can remain unchanged. However, if liraglutide is added to a sulfonylurea alone or in combination with metformin, a reduction in the dosage of the sulfonylurea should be considered to decrease the risk of hypoglycaemia. Although self-monitoring of glucose levels is not necessary for liraglutide, it may be required for patients receiving concomitant sulfonylurea therapy.[7] According to the US prescribing information, when liraglutide treatment is initiated, a reduction in the dose of concomitantly administered insulin secretagogues (such as sulfonylureas) should be considered to reduce the risk of hypoglycaemia.[8]

No adjustment of liraglutide dose is required for elderly (aged >65 years) patients, although therapeutic experience is limited in patients aged ≥75 years.[7] Dose adjustment is also not required for patients with mild renal impairment (creatinine clearance [CL_{CR}] 60–90 mL/min; 3.6–5.4 L/h).[7] However, as treatment experience of patients with moderate renal impairment (CL_{CR} 30–59 mL/min [1.8–3.54 L/h]) is limited and there is no experience of the treatment of patients with severe renal impairment (CL_{CR} <30 mL/min [<1.8 L/h]), lir-

aglutide is not recommended for these populations, including those with end-stage renal disease.[7] In the US prescribing information, it is stated that liraglutide should be used with caution in patients with renal impairment, with no specific dosage recommendations provided.[8] Therapeutic use of liraglutide in patients with mild, moderate or severe hepatic impairment is limited and it is therefore not recommended[7] or should be used with caution[8] in these populations. Liraglutide is not recommended for the treatment of patients aged <18 years because of a lack of clinical data in these patient populations.[7,8] If pancreatitis is suspected, liraglutide and other drugs that could potentially be associated with pancreatitis should be discontinued and liraglutide treatment should not be restarted if pancreatitis is confirmed. Liraglutide should be used with caution in patients with a history of pancreatitis.[7,8] Local prescribing information should be consulted for contraindications, warnings and precautions relating to the use of liraglutide.

8. Place of Liraglutide in the Management of Type 2 Diabetes Mellitus

Type 2 diabetes is a common and progressive disease characterized by decreased insulin secretion and sensitivity, and impaired β-cell function. Central to the management of type 2 diabetes is good glycaemic control, which leads to a reduction in the risk of patients developing clinical sequelae of diabetes, including microvascular, neuropathic and macrovascular complications, i.e. cardiovascular disease. Although lifestyle interventions, including improvements in diet and increased exercise, are an important initial step in the management of patients with type 2 diabetes, pharmacological management with at least one antihyperglycaemic agent is usually required because of the progressive nature of the disease. When managing patients with type 2 diabetes, a target HbA_{1c} level of <7% is recommended in consensus guidelines from the ADA and the European Association for the Study of Diabetes (EASD).[75,96]

Among the available OADs, metformin, a biguanide that reduces hepatic glucose production and improves insulin sensitivity, is recommended as first-line therapy for patients needing drug treatment despite lifestyle modification. However, although metformin is effective for many patients, an alternative drug is required for patients unable to tolerate the gastrointestinal adverse effects that are associated with its use. For such patients, a sulfonylurea (e.g. glibenclamide, glimepiride) with a different mechanism of action (increased endogenous insulin release) may be a suitable alternative first-line treatment; a sulfonylurea may also be used in combination with metformin for patients requiring a dual regimen for effective glycaemic control. Consensus guidelines also recommend insulin as an alternative to a sulfonylurea in combination with metformin.[96] However, both the sulfonylureas and insulin may produce bodyweight gain, and hypoglycaemia is a potentially serious and relatively common adverse effect of treatment with both drug classes. Other agents that may be used in combination with metformin include the insulin-sensitizing thiazolidinediones (e.g. rosiglitazone, pioglitazone);[96] while effective, these agents are also associated with bodyweight gain, fluid retention and an increased risk of cardiac failure. In the EU, rosiglitazone and fixed-dose combinations of rosiglitazone/glimepiride and rosiglitazone/metformin have been suspended from use by the European Medicines Agency because of concerns relating to cardiovascular safety.[97] Pioglitazone has recently been reported to be associated with a small risk of bladder cancer.[98] The glinides (e.g. nateglinide and repaglinide), DPP-4 inhibitors (e.g. sitagliptin and vildagliptin), alpha-glucosidase inhibitors (e.g miglitol, acarbose) and the GLP-1 analogues (e.g. liraglutide and exenatide) are among the other drugs approved widely for the treatment of patients with type 2 diabetes.

The ability of a drug to reduce the HbA_{1c} level as well as tolerability profile and cost are among the many factors that must be considered when selecting an antidiabetic drug, with treatment individualization key to successful patient management. For example, when treating a patient with an HbA_{1c} level close to normal, it may be appropriate to select a drug with a low propensity to produce hypoglycaemia as an adverse event.

Importantly, while many traditional therapies provide effective glycaemic control, at least in the short-term, the majority do not avert the natural course of the disease, preserve or improve β-cell function, produce clinically relevant bodyweight loss or address cardiovascular risk factors. Incretin therapies, such as the DPP-4 inhibitors and the GLP-1 analogues, have been developed to meet some of these challenges. In addition to the beneficial effects of these agents on β-cell function, drugs in these classes have been shown to increase satiety and promote bodyweight loss or stabilize bodyweight. As such, incretin-based therapies are recommended in ADA/EASD[96] and American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE)[99] treatment algorithms for treatment-naive and previously treated patients with type 2 diabetes rather than being restricted to third- or fourth-line treatment options.[100]

Liraglutide is a GLP-1 analogue that targets the incretin system by exploiting the physiological effects of native GLP-1, which has an important role in glucose homeostastis (section 2). A summary of the key features of liraglutide is presented in table X.

Differences in the structure of liraglutide compared with native GLP-1 allow it to self-associate after subcutaneous administration and bind reversibly to serum albumin, thereby reducing its susceptibility to degradation to DPP-4 and prolonging its half-life to ≈13 hours, making it suitable for once-daily administration, while retaining 97% homology to native GLP-1. Because of close similarity to native GLP-1, liraglutide has a low propensity to produce anti-liraglutide antibodies (incidence <10%) and this does not appreciably affect its efficacy. By contrast, exenatide, the first GLP-1 analogue approved by the FDA for the treatment of type 2 diabetes, has 53% homology to native GLP-1 and has been shown to be associated with anti-exenatide antibodies in ≈50% of patients, which is thought to have a negative effect on its efficacy in the treatment of type 2 diabetes (section 2).

Treatment with liraglutide led to improvements in glycaemic control in patients with type 2 diabetes in numerous randomized, comparative trials in various patient populations in which the change from baseline in plasma HbA_{1c} levels was the primary endpoint. Six of these trials were conducted as part of the LEAD programme, which evaluated the efficacy of liraglutide monotherapy or combination therapy across a continuum of management for adults with type 2 diabetes. Across these trials, reductions in HbA_{1c} levels ranged from −1.0% to −1.5% for recipients of liraglutide 1.2 or 1.8 mg as monotherapy or combination therapy. Liraglutide was generally more effective than comparators in improving other glycaemic parameters, including fasting blood glucose and PPG. Early and sustained treatment effects were achieved with liraglutide, with significant reductions in HbA_{1c} and FPG levels achieved within, respectively, 8 and 2 weeks of the addition of liraglutide 1.2 or 1.8 mg to OAD treatment, in a pooled analysis of data from LEAD-1, -2 and -4 trials.[101] In addition, liraglutide as monotherapy or combination therapy improved other efficacy (secondary) endpoints, including indices of β-cell function and produced early clinically meaningful reductions in bodyweight (section 4)[101] across a broad range of body mass index values.[102,103] Reductions in other cardiovascular risk factors were also improved, including SBP and some components of the lipid profile in several of the phase III trials. In guidelines from the UK National Institute

Table X. Subcutaneous liraglutide in adults with type 2 diabetes mellitus: a summary

Acylated analogue of GLP-1 with 97% homology to GLP-1
Associated with a low incidence (<10%) of anti-liraglutide antibodies
Elimination half-life of ≈13 h, allowing for once-daily administration
Administered without regard to meals
Produces rapid and sustained glycaemic control
Reduces HbA_{1c} levels and improves other glycaemic parameters e.g. reduces fasting plasma glucose levels
Improves β-cell function
Reduces bodyweight
Reduces systolic blood pressure
May be administered with metformin and/or a sulfonylurea, or with metformin and a thiazolidinedione
Most common adverse events are mild or moderate nausea, diarrhoea and headache
Cost effective as add-on therapy in combination with one or two OADs compared with rosiglitazone or exenatide

GLP-1 = glucagon-like peptide-1; **HbA_{1c}** = glycosylated haemoglobin; **OAD** = oral antidiabetic drug.

for Health and Clinical Excellence, liraglutide 1.2 mg once daily as a component of triple therapy in combination with metformin and a sulfonylurea, or metformin and a thiazolidinedione, is a recommended treatment option for certain patients with type 2 diabetes.[104] The 1.8 mg once daily dosage is not recommended as the guidelines state that there is no evidence to show better efficacy with the higher than lower 1.2 mg dose.[104]

Although the efficacy of liraglutide is well established, further longer term studies evaluating the durability of effects on glycaemic control are of interest, as are trials (e.g. the LEADER [Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results – A Long Term Evaluation] trial) evaluating the relative effects of liraglutide and other GLP-1 agonists on cardiovascular parameters to determine which may provide the greatest reduction in cardiovascular risk. As well as the beneficial effects on bodyweight shown by liraglutide in patients with type 2 diabetes, liraglutide, at dosages up to 3 mg once daily, has also shown potential as a treatment for bodyweight loss in nondiabetic patients,[105,106] although it is not approved for use in this indication.

Intensive treatment for patients with type 2 diabetes can have a negative effect on patient perceptions of treatment, even when clinical outcomes are improved.[80] Indeed, health-related quality of life in this patient population may be sensitive to a number of variables, including complex treatment regimens, treatment-related adverse events, glycaemic control and increasing bodyweight. Therefore, patient-reported outcome data, complementing clinical evaluations of new treatments for type 2 diabetes, are of interest, particularly as patient perception and satisfaction may affect treatment adherence.[80,81] Patient satisfaction with liraglutide treatment was significantly greater than with sitagliptin (each in combination with metformin), possibly as a result of perceptions of greater HbA_{1c} reduction and bodyweight loss with liraglutide. Patient perception of a lower incidence of hypoglycaemia with liraglutide plus metformin than with metformin monotherapy was a reason for patients being more satisfied with the liraglutide regimen in another study of similar design. Better glycaemic control and decreased bodyweight with liraglutide than with glimepiride resulted in improved psychological and emotional well-being in liraglutide recipients in another study (section 4.3). Across the phase III clinical trials, liraglutide as monotherapy or combination therapy was generally well tolerated. Most adverse events were gastrointestinal and of mild or moderate severity. Liraglutide was also associated with a low risk of hypoglycaemia. Few cases of acute pancreatitis have been reported. Whether liraglutide causes thyroid C-cell tumours in humans is a focus of ongoing research.

Liraglutide combination therapy was a cost-effective treatment compared with rosiglitazone or glimepiride combination therapy (section 6). Nevertheless, further well designed studies are needed as pharmacoeconomic studies in general are subject to limitations.

New developments in this therapeutic area include fixed-dose combinations of GLP-1 agonists and long-acting insulin analogues, a once-weekly formulation of exenatide, noninjectable formulations of GLP-1 agonists and new GLP-1 agonists e.g. lixesenatide; comparisons of these new treatments with liraglutide in controlled clinical trials will be of interest in the future.

In conclusion, liraglutide has an important place in the management of adults with type 2 diabetes across a continuum of care. As well as providing effective glycaemic control, liraglutide improves pancreatic β-cell function and leads to bodyweight loss, thereby addressing some of the unmet needs of patients treated with traditional OADs.

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