original article

ORIGINAL ARTICLE

Comparison of insulin glargine and liraglutide added to oral agents in patients with poorly controlled type 2 diabetes

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Aim: To compare safety and efficacy of insulin glargine and liraglutide in patients with type 2 diabetes (T2DM).

Methods: This randomized, multinational, open-label trial included subjects treated for T2DM with metformin ± sulphonylurea, who had glycated haemoglobin (HbA1c) levels of 7.5–12%. Subjects were assigned to 24 weeks of insulin glargine, titrated to target fasting plasma glucose of 4.0–5.5 mmol/L or liraglutide, escalated to the highest approved clinical dose of 1.8 mg daily. The trial was powered to detect superiority of glargine over liraglutide in percentage of people reaching HbA1c <7%.

Results: The mean [standard deviation (s.d.)] age of the participants was 57 (9) years, the duration of diabetes was 9 (6) years, body mass index was 31.9 (4.2) kg/m^2 and HbA1c level was 9.0 (1.1)%. Equal numbers ($n = 489$) were allocated to glargine and liraglutide. Similar numbers of subjects in both groups attained an HbA1c level of <7% (48.4 vs. 45.9%); therefore, superiority of glargine over liraglutide was not observed (p = 0.44). Subjects treated with glargine had greater reductions of HbA1c [−1.94% (0.05) and −1.79% (0.05); p = 0.019] and fasting plasma glucose [6.2 (1.6) and 7.9 (2.2) mmol/L; p < 0.001] than those receiving liraglutide. The liraglutide group reported a greater number of gastrointestinal treatment-emergent adverse events (p < 0.001). The mean (s.d.) weight change was +2.0 (4.0) kg for glargine and −3.0 (3.6) kg for liraglutide (p < 0.001). Symptomatic hypoglycaemia was more common with glargine (p < 0.001). A greater number of subjects in the liraglutide arm withdrew as a result of adverse events (p < 0.001).

Conclusion: Adding either insulin glargine or liraglutide to subjects with poorly controlled T2DM reduces HbA1c substantially, with nearly half of subjects reaching target levels of 7%.

Keywords: insulin glargine, liraglutide, type 2 diabetes

Introduction

There is currently no widely accepted paradigm for the sequence of therapy in type 2 diabetes mellitus (T2DM), although several sets of guidelines have recently been proposed [1–3]. Most experts agree that metformin is the drug of first choice for T2DM, with a variety of oral and injectable therapies available when glycaemic control is not attained, or is lost, with this initial approach; however, because injections are considered by some to be more difficult to initiate than tablets [4], injectable drugs are usually considered only after two or more oral agents have been started, and then not until the glycated haemoglobin (HbA1c) level is substantially elevated

or patients become symptomatic. The progressive nature of T2DM [5–8] and inertia in advancing therapy are major problems contributing to poor glycaemic control for many patients [9,10].

Although insulin remains the most commonly used injectable therapy for T2DM, the last decade has brought drugs based on glucagon-like peptide-1 (GLP-1), a naturally occurring product of the intestine. Activation of the GLP-1 receptor stimulates insulin secretion, inhibits glucagon release, delays gastric emptying, reduces hepatic glucose production and causes satiety [11]. In controlled trials, both basal insulin and GLP-1 receptor agonists effectively lowered glucose in patients not reaching glycaemic targets on oral agents [12,13]. These studies were conducted in subjects with good to moderate glycaemic control and HbA1c levels ∼8%. The present Efficacy Assessment of Insulin Glargine vs. Liraglutide after Oral Agent Failure (EAGLE) trial compared a basal insulin, insulin glargine, with a GLP-1 receptor agonist, liraglutide, in a cohort of people with T2DM with poor glycaemic control,

representative of the population that is frequently started on injectable drugs. As insulin treatment can be well titrated, while GLP-1 receptor agonists are delivered at a fixed dose, we hypothesized that in poorly controlled patients insulin glargine would be superior to liraglutide.

Methods

Study Design

The EAGLE study was a multicentre, international, 24-week, comparative, two-arm, parallel, randomized (1 : 1), open-label trial conducted in 17 countries (Table S1) from August 2010 to October 2012. The comparative study consisted of a 2-week screening period and a 24-week treatment period with insulin glargine or liraglutide (Figure 1). Eligible subjects were allocated to liraglutide or insulin glargine randomly through a central co-ordinating centre in the order in which they qualified for the study, and stratified by site to ensure a balance in each treatment group (1 : 1 ratio). Neither participants nor investigators were masked to group assignment. The study was conducted in accordance with the Declaration of Helsinki and the Guidelines on Good Clinical Practice. Every centre obtained local research ethics committee approval and all participants gave full informed written consent before entry into the study. The comparative study was followed by a 24-week extension phase with a switch to insulin glargine in subjects not adequately controlled with liraglutide (Figure 1) that ended in March 2013.

Subjects

Participants who were aged 35–75 years with a diagnosis of T2DM for ≥ 1 year were eligible if they had an HbA1c level >7.5 and $\leq 12\%$ (>58 and ≤ 108 mmol/mol), had a body mass index between 25 and 40 kg/m^2 and were willing to comply with study requirements. To be eligible, subjects were also required to be on metformin at a minimum dose of 1 g/day, alone or in combination with sulphonylurea, glinides or a dipeptidyl peptidase-4 inhibitor for >3 months. Those treated with GLP-1 receptor agonists or insulin in the previous year, or with thiazolidinediones or α-glucosidase inhibitors in the previous 3 months were excluded. Other exclusion criteria included impaired renal (estimated glomerular filtration rate <60 ml/min) or hepatic (alanine aminotransferase/ aspartate aminotransferase >2.5 × upper limit of normal) function, or any condition that investigators felt would compromise the patient's safety or participation in the study. Subjects receiving liraglutide who had fasting plasma glucose levels ≥ 13.9 mmol/L at weeks 12 or 18 (early switch), or HbA1c levels $\geq 7.0\%$ at week 24 of the comparative study were eligible to be switched to insulin glargine for a 24-week study extension.

Procedures

Clinic visits were for screening, randomization (week 0) and follow-up at weeks 2, 6, 12, 18 and 24, with telephone contacts at weeks 1, 3, 4, 8 and 10. All participants received a glucose meter (Accu-Chek Aviva or Performa; Roche Diagnostics Ltd, Basel, Switzerland) to record self-monitored glucose values. Individuals randomized to insulin glargine were instructed on a titration schedule, adjusted every 3 days, to attain fasting plasma glucose levels of ≥ 4.0 and ≤ 5.5 mmol/l (Table S2). Self-monitored glucose values and insulin doses were reviewed electronically by an International Titration Committee during the trial and study investigators contacted if titration was inadequate.

The initial dose of liraglutide was 0.6 mg once daily injected subcutaneously in the morning or evening using a prefilled pen. The dose was then increased to 1.2 and 1.8 mg daily at weekly intervals if it was well tolerated; doses could be reduced to 1.2 mg in subjects having difficulty with the higher dose. In both groups, metformin continued at a stable dose, and sulphonylureas were reduced or discontinued at the investigator's discretion. Glinides and dipeptidyl peptidase-4 inhibitors were stopped at randomization.

Participants' HbA1c levels were recorded at baseline, weeks 12 and 24, while seven-point plasma glucose profiles (before and 2 h after breakfast, lunch, dinner and at bedtime) were recorded over three consecutive days before clinic visits at weeks 0, 12 and 24. Body weight was recorded at weeks 0, 2, 6, 12, 18 and 24. HbA1c and other laboratory blood tests were analysed at a central laboratory.

The study was powered to show the superiority of insulin glargine over liraglutide in terms of the percentage of subjects reaching an HbA1c target of <7% over 24 weeks. Secondary outcomes included change in HbA1c and self-monitored blood glucose levels. Safety outcomes were treatment-emergent adverse events (TEAEs) reported by the patient or noted by the investigator, standard blood chemistry, body weight, vital signs and hypoglycaemia. Adverse events were not specifically adjudicated, and discontinuation of the drug was based on the standard recommendations accompanying drug approval. Symptomatic hypoglycaemia was defined as an event with typical symptoms, with or without an associated plasma glucose level <4.0 mmol/L. Severe symptomatic hypoglycaemia was defined as episodes requiring assistance from another person associated with a measured plasma glucose level <2.0 mmol/L or, in the absence of a plasma glucose measurement, with prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration. Treatment satisfaction and quality of life were measured using the diabetes treatment satisfaction questionnaire (DTSQ) and the audit of diabetes-dependent quality of life (ADDQoL), respectively [14,15]. Eligible subjects in the liraglutide arm (early switch or HbA1c $\geq 7\%$ at the end of the comparative phase) consenting to take part in the extension to the study had clinic visits at weeks 30, 36 and 48 and intervening telephone contacts (Figure 1). Liraglutide was discontinued, insulin glargine started and the dose titrated in an identical manner to that used in the comparative trial.

Statistical Analysis

Data analysis was performed using SAS version 9.2. All data are expressed as mean [standard deviation (s.d.)], median (quartile 1 and quartile 3), estimates [standard error (s.e.)] or differences with 95% confidence interval (CI) as appropriate. Missing values were imputed using the last observation carried forward
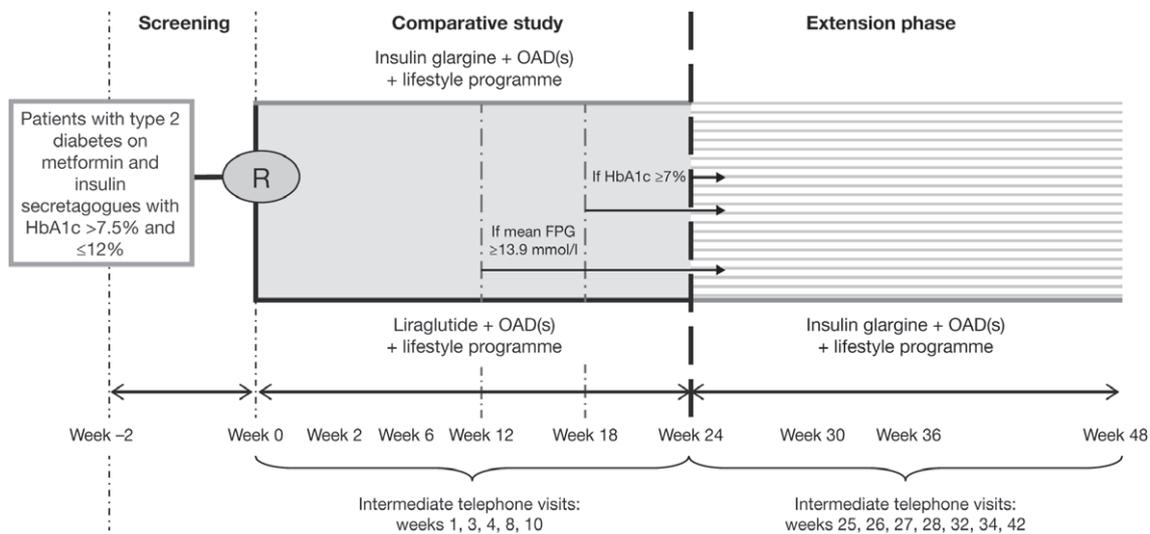
Figure 1. Study design. HbA1c, glycated haemoglobin; R, randomization; FPG, fasting plasma glucose; OAD(s), oral antidiabetic drug(s).

method. The modified intent-to-treat population included all participants randomly assigned to treatment groups who had received at least one dose of the study drug and had at least one on-treatment assessment of any primary or secondary efficacy variable, irrespective of compliance with the study protocol and procedures. All participants randomized and treated were included in the safety population for analysis.

The superiority of insulin glargine in terms of the percentage of participants reaching the HbA1c target of <7% at the end of the study was tested using a chi-squared test at 5% level; two-sided 95% CIs of the differences in success rates (insulin glargine – liraglutide) were also calculated. In the event that superiority was not demonstrated, there was an *a priori* plan to test for non-inferiority of insulin glargine, defined by a lower limit of the two-sided 95% CI > −3.5% of the rate measured with liraglutide. Assuming a success rate of 46% with insulin glargine and 35% with liraglutide and a 10% rate of non-evaluable participants, a sample of 930 evaluable participants (465 per arm) was estimated to be necessary to demonstrate superiority of insulin glargine with a two-sided α risk of 5 and 90% power.

For categorical variables, Pearson chi-square or Fisher's exact test were used. The rate of hypoglycaemia per patient-year was analysed using a generalized linear model based on a Poisson, negative binomial, zero-inflated Poisson or zero-inflated negative binomial distribution. The best model was fitted according to the likelihood ratio test and Vuong test.

Results

Disposition of Subjects

Of 1456 participants initially screened, 978 were randomized to insulin glargine ($n = 489$) or liraglutide ($n = 489$; Figure S1). The completion rate was higher with insulin glargine (91.4%) than with liraglutide (84.7%). A total of 67 subjects (13.7%) treated with liraglutide and 37 (7.6%) treated with insulin glargine withdrew prematurely ($p < 0.001$), including

34 (7.1%) and 6 (1.2%), respectively, for adverse events ($p < 0.001$). The two treatment groups had similar baseline characteristics (Table 1). Participants had a mean (s.d.) HbA1c of 9.0 (1.1)% [76 (12) mmol/mol] and a median duration of diabetes of 8.5 years.

Doses of Insulin Glargine and Liraglutide

At treatment onset the mean (s.d.) daily dose of insulin was 0.15 (0.05) U/kg [13.4 (4.9) U/day], and increased to 0.54 (0.31) U/kg [51.7 (34.1) U/day] at 24 weeks. The mean daily dose of liraglutide at the conclusion of the study was 1.71 (0.24) mg. All subjects continued metformin except for one in the insulin glargine group. Sulphonylureas were initially taken by 286 (60%) of those on insulin glargine and by 298 (63%) receiving liraglutide. At 24 weeks, 240 (49%) and 235 (48%), respectively, were still taking them.

Glycaemic Control

At the end of the comparative study, 226 (48.4%) of 467 participants on insulin glargine had HbA1c < 7% compared with 210 (45.9%) of 458 participants on liraglutide. The difference (insulin glargine–liraglutide) was 2.5% (95% CI −3.9, 8.9%; $p = 0.44$); therefore, superiority of insulin glargine was not observed, nor was non-inferiority of glargine to liraglutide ($p = 0.066$). The mean (s.d.) HbA1c level at the end of the comparative study was 7.1 (1.0)% [54 (11) mmol/mol] with insulin glargine and 7.3(1.1)% [56 (12) mmol/mol] with liraglutide (Figure 2A), with adjusted mean (s.e.) changes of −1.94 (0.05)% for those on glargine and −1.79 (0.05)% for those on liraglutide. The adjusted mean difference in HbA1c at the end of the study was −0.15% (95% CI: −0.28 to −0.02; $p = 0.019$). The effects of insulin glargine and liraglutide did not differ across the range of baseline HbA1c values among the study subjects (Table S3). The absolute reduction in HbA1c was progressively greater from the lowest to the highest quartiles of baseline values, but the relative effectiveness was comparable with both treatments.

Table 1. Baseline clinical characteristics of patients included in efficacy analysis (modified intent-to-treat population) – comparative study.

	Insulin glargine group, $N = 474$	Liraglutide group, $N = 470$
Mean (s.d.) age, years	57.1 (8.8)	57.4 (8.9)
Women, *n* (%)	224 (47.3)	207 (44.0)
Mean (s.d.) body weight, kg	90.8 (16.6)	90.1 (16.7)
Mean (s.d.) body mass index, kg/m^2	32.0 (4.2)	31.8 (4.1)
Median (Q1; Q3) duration of diabetes, years	8.5 (0.9; 34.8)	8.4 (1.0; 33.5)
Mean (s.d.) systolic blood pressure, mmHg	133.2 (15.4)	133.8 (15.5)
Mean (s.d.) diastolic blood pressure, mmHg	80.6 (9.6)	80.5 (8.8)
Mean (s.d.) heart rate, beats/min	74.9 (9.9)	74.6 (9.8)
Median (Q1; Q3) duration of OADs, years	7.2 (0.3; 29.0)	6.8 (0.3; 29.7)
Mean (s.d.) dose of metformin, mg	1939 (557)	1955 (526)
Any late diabetes complication, *n* (%)	212 (44.7)	223 (47.4)
Macrovascular disease, *n* (%)		
Myocardial infarction	19 (4.0)	19 (4.0)
Angina pectoris	24 (5.1)	26 (5.5)
Coronary artery disease	47 (9.9)	55 (11.7)
Heart failure	4 (0.8)	8 (1.7)
Stroke	9 (1.9)	10 (2.1)
Transient ischaemic attack	4 (0.8)	11 (2.3)
Peripheral vascular disease	34 (7.2)	42 (8.9)
Microvascular disease, *n* (%)		
Diabetic neuropathy	130 (27.4)	143 (30.4)
Diabetic nephropathy	42 (8.9)	46 (9.8)
Diabetic retinopathy	42 (8.9)	40 (8.5)
Any prior antidiabetes medication, *n* (%)	473 (99.8)	469 (99.8)
Metformin	472 (99.6)	469 (99.8)
Sulphonylurea	320 (67.5)	321 (68.3)
Dipeptidyl peptidase-4 inhibitors	100 (21.1)	100 (21.3)
Glinides	14 (3.0)	16 (3.4)
Alpha-glucosidase inhibitors	1 (0.2)	1 (0.2)
Thiazolidinediones	1 (0.2)	1 (0.2)
Mean (s.d.) HbA1c, % mmol/mol	9.0 (1.0)	9.1 (1.1)
	75 (11)	76 (12)
Mean (s.d.) self-monitored fasting plasma glucose, mmol/L	9.8 (2.6)	9.9 (2.6)
Mean (s.d.) total cholesterol, mmol/L	4.6 (1.1)	4.5 (1.1)
Mean (s.d.) LDL cholesterol, mmol/L	2.6 (1.0)	2.6 (0.9)
Mean (s.d.) HDL cholesterol, mmol/L	1.2 (0.3)	1.2 (0.3)
Mean (s.d.) triglycerides, mmol/L	2.3 (1.8)	2.3 (1.6)
Mean (s.d.) aspartate aminotransferase, U/L	23.7 (11.0)	24.0 (11.3)
Mean (s.d.) alanine aminotransferase, U/L	31.5 (15.7)	31.5 (16.7)
Mean (s.d.) serum creatinine, μmol/L	75.9 (16.9)	76.8 (16.5)
Concomitant treatments (other than oral antidiabetic drugs), *n* (%)		
Any	449 (92.8)	453 (93.8)
Antihypertensive agents, *n* (%)		
β-blockers	113 (23.3)	115 (23.9)
Calcium-channel blockers	88 (18.2)	76 (15.8)
Agents acting on renin-angiotensin system	317 (65.5)	315 (65.5)
Lipid-modifying agents	306 (63.2)	294 (61.1)
Antithrombotic agents	191 (39.5)	189 (39.3)

HbA1c, glycated haemoglobin; s.d., standard deviation.

Mean (s.d.) self-monitored fasting glucose was significantly lower with insulin glargine than with liraglutide at 24 weeks [6.2 (1.6) and 7.9 (2.2) mmol/L; p < 0.001; Figure 2B], as was mean daily plasma glucose [8.1 (1.6) and 8.6 (2.2) mmol/L; p < 0.001; Figure 2C).

Safety

Treatment-emergent adverse events were reported by 317 (65.9%) of 481 participants in the liraglutide group and 243 (50.2%) of 484 participants in the insulin glargine group (p < 0.001; Table 2). More gastrointestinal TEAEs were reported with liraglutide, including nausea (30.4 vs. 2.7%), vomiting (9.6 vs.1.7%) and diarrhoea (12.9 vs. 3.7%; all p < 0.001). Serious TEAEs were reported by 11 (2.3%) subjects on insulin glargine and 15 (3.1%) on liraglutide, with each type of event reported by only one individual (Table S4). One case of acute pancreatitis was reported with liraglutide. Six (1.2%) of the 484 participants in the insulin glargine group and 34 (7.1%) of the 481 participants in the liraglutide group withdrew from the study because of a TEAE (Table S5).
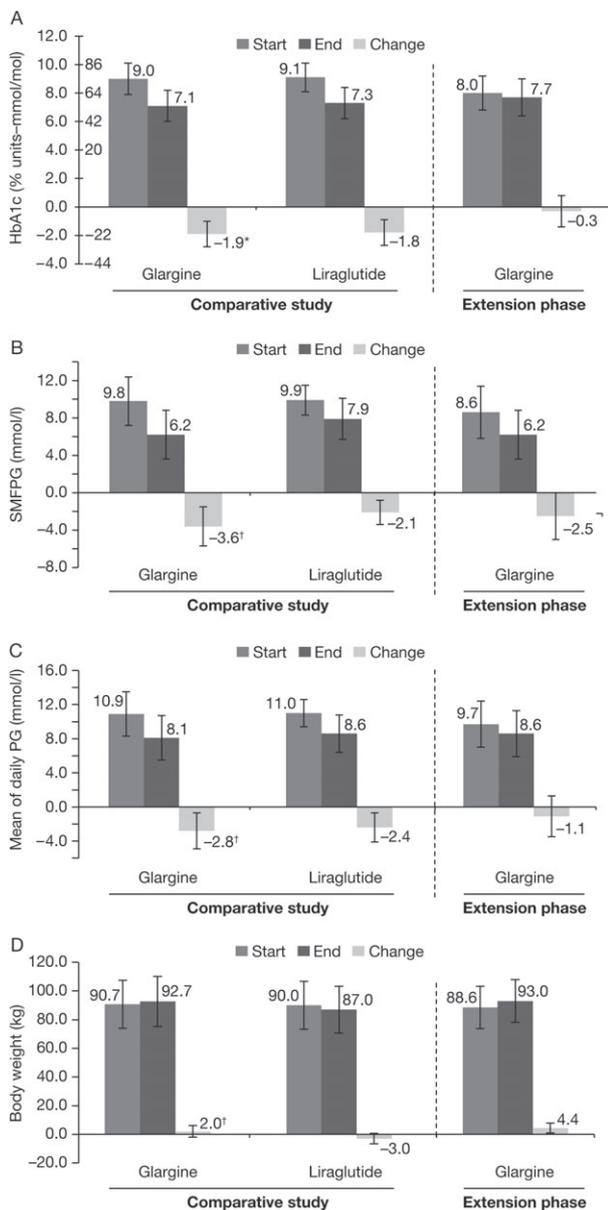
Figure 2. (A) Glycated haemoglobin (HbA1c), (B) self-monitored fasting plasma glucose (SMFPG), (C) mean daily plasma glucose (PG) and (D) body weight during the comparative study and extension phase. Subjects treated with liraglutide who had fasting plasma glucose ≥13.9 mmol/l at weeks 12 or 18 (early switch) or had HbA1c ≥7.0% (≥53 mmol/mol) at week 24 of the comparative study were eligible to be switched to insulin glargine and to be included in the 24-week extension phase. *p = 0.019; †p < 0.001 compared with liraglutide.

Body weight increased in the insulin glargine group [2.0 (4.0) kg] and decreased in the liraglutide group [3.0 (3.6) kg; Figure 2D]; the adjusted mean difference was 4.9 kg (95% CI 4.41–5.37; p < 0.001). More participants in the insulin glargine group (45%) had symptomatic hypoglycaemia than in the liraglutide group (18%; Table 3). Severe symptomatic hypoglycaemia did not occur in participants on insulin glargine and occurred in two participants on liraglutide. No severe nocturnal symptomatic hypoglycaemia was reported in either group.

Table 2. Treatment-emergent adverse events (>5% in either group) in the comparative study safety population.

	Insulin glargine group, N = 484	Liraglutide group, N = 481	p
Any class	243 (50.2)	317 (65.9)	<0.001
Gastrointestinal disorders			
Nausea	13 (2.7)	146 (30.4)	<0.001
Diarrhoea	18 (3.7)	62 (12.9)	<0.001
Vomiting	8 (1.7)	46 (9.6)	<0.001
Constipation	6 (1.2)	26 (5.4)	<0.001
Dyspepsia	4 (0.8)	25 (5.2)	<0.001
Infections and infestations			
Nasopharyngitis	38 (7.9)	35 (7.3)	0.736
Nervous system disorders			
Headache	24 (5.0)	29 (6.0)	0.466
Metabolism and nutrition disorders			
Decreased appetite	1 (0.2)	45 (9.4)	<0.001

n (%), number and percentage of patients with at least one adverse event.

Systolic blood pressure was reduced (−3.1 mmHg) with liraglutide, while no changes were noted with insulin glargine. Change in heart rate from baseline was significantly different between insulin glargine [−0.5 (9.4) bpm] and liraglutide [+2.6 (9.6) bpm]; the adjusted mean difference was −3.1 bpm (95% CI −4.2, −2.1; p < 0.001; Table S6). Changes in cholesterol and triglycerides were similar between treatment groups.

Quality-of-life perception improved in both groups and was similar between the two treatment groups.

Extension Phase

A total of 210 subjects in the liraglutide group were eligible for the extension phase and, of these, 160 (75.2%) participated (subject characteristics in Table S7). The modified intent-to-treat population, defined as those treated with ≥1 dose of insulin glargine and with ≥1 assessment of efficacy after extension entry, comprised 154 subjects; the safety population comprised 160 subjects treated with at least one dose of glargine in the extension phase. At the start of the extension phase, all 160 subjects were taking metformin, 89 (56%) were taking a sulphonylurea and their mean HbA1c level was 8.0 (0.9)% [64 (10) mmol/mol].

The mean (s.d.) dose of insulin increased from 0.18 (0.04) U/kg [15.8 (4.5) U/day] at the start, to 0.55 (0.29) U/kg [50.9 (27.1) U/day] at the conclusion, of the extension phase. The mean HbA1c level decreased to 7.7 (0.9)% [61 (10) mmol/mol], giving a mean change of −0.3 (1.1)% [−3 (12) mmol/mol; Figure 2A], with 35 subjects (23%) reaching an HbA1c level <7%. There were also decreases in self-monitored fasting blood glucose (Figure 2B) and mean daily blood glucose (Figure 2C). Body weight increased by 4.4 (3.5) kg over the course of the extension phase (Figure 2D). The incidence of symptomatic hypoglycaemia was 35.6%, with nocturnal hypoglycaemia in 13.8%, but no reports of severe hypoglycaemia. Sixty-three subjects (39.4%) experienced a TEAE, with 5 (3.1%) experiencing a serious TEAE and 2 (1.3%) experiencing a TEAE that led them to discontinue glargine (Table S8).

Table 3. Rate of symptomatic, severe and nocturnal hypoglycaemia during 24-week treatment with glargine or liraglutide – comparative study (safety population).

	Insulin glargine group N =484		Liraglutide group N =481		Insulin glargine/liraglutide for events per patient-year		
	Patients with ≥1 event*, n (%)	Estimated event rate (s.e.) per patient-year	Patients with ≥1 event*, n (%)	Estimated event rate (s.e.) per patient-year	Estimated rate ratio	95% CI	p
All symptomatic hypoglycaemia	219 (45.2)	7.6 (1.8)	85 (17.7)	1.9 (0.6)	4.0	2.9–5.6	<0.0001
Symptomatic hypoglycaemia with plasma glucose ≤3.9 mmol/L	200 (41.3)	5.1 (0.6)	66 (13.7)	1.1 (0.1)	4.7	3.4–6.6	<0.0001
Nocturnal symptomatic hypoglycaemia	90 (18.8)	1.4 (0.2)	15 (3.1)	0.1 (0.0)	15.0	8.2–27.5	<0.0001
Nocturnal symptomatic hypoglycaemia with plasma glucose ≤ 3.9 mmol/L (70 mg/dL)	80 (16.5)	1.3 (0.2)	14 (2.9)	0.1 (0.0)	15.0	8.2–28.5	<0.0001
Severe symptomatic hypoglycaemia	0	0	2 (0.4)	—	0.0	0.0–NE	1.0*
Severe nocturnal symptomatic hypoglycaemia	0	0	0	0	—	—	—
Symptomatic hypoglycaemia with plasma glucose ≤ 3.1 mmol/L (56 mg/dL)	101 (20.9)	1.2 (0.2)	26 (5.4)	0.3 (0.0)	4.7	2.9–7.5	<0.0001
Nocturnal symptomatic hypoglycaemia with plasma glucose ≤ 3.1 mmol/L (56 mg/dL)	41 (8.5)	0.4 (0.1)	5 (1.0)	0.0 (0.0)	13.4	5.1–34.9	<0.0001

s.e., standard error.

The safety population consisted of all participants randomly assigned to treatment groups and treated. Estimated rate ratios and p values were derived from a binomial negative model with the exception of that denoted by *, which was from a Poisson model.

Discussion

This trial was designed to compare the effects of two injectable medications in subjects with T2DM who were not achieving adequate glycaemic control with oral therapy. In this population with poor glycaemic control, both adequately titrated glargine and liraglutide targeted to the highest approved daily dose were effective and reduced HbA1c to the predefined target level of 7% in nearly half the subjects. While glargine caused a statistically significant greater reduction in HbA1c, the relative benefit was small (0.15%) and both treatments approached mean HbA1c reductions of 2% (−1.9% for glargine; −1.8% for liraglutide). Overall the treatments were well tolerated, with use of glargine causing more weight gain and hypoglycaemia, and a higher dropout rate and more gastrointestinal side effects with the use of liraglutide. Based on these results, it appears that addition of once daily injectable therapy is a sound strategy to improve glycaemic control in patients with high HbA1c levels on oral therapy.

The subjects in the present study were recruited from multiple sites around the world, and included overweight and obese people, most using more than one oral agent, with mean HbA1c levels of ~9%. This cohort exemplifies patients commonly encountered in clinical practice in whom glycaemic control is so poor that the need to intensify therapy is unambiguous, and the starting HbA1c values fit with the level where many physicians consider starting an injectable medication. Of the studies currently available that have compared GLP-1 receptor agonists with insulin glargine, the present EAGLE study cohort had the highest baseline HbA1c [13,16]. Thus, the study population is a key feature of this trial, representative as it is of patients with T2DM clearly requiring additional treatment and making the results readily applicable to clinical practice.

We predicted that insulin glargine would be the more effective agent for lowering HbA1c in the present trial because the dose can be titrated continuously to achieve glycaemic targets. In fact, titration of glargine in this trial was effective based on the mean fasting glucose of 6.2 mmol/L reached in the insulin-treated cohort, a level lower than other studies using similar insulin treatment algorithms [17,18]. Accordingly,

the decrease in HbA1c level in the present study was greater than that in other treat-to-target studies, and the percentage of subjects reaching the HbA1c target of 7% was similar, despite higher starting baseline values. The effect of liraglutide with regard to the primary endpoint was also greater in the present EAGLE study than in previous studies [13,16], and the effect on HbA1c only slightly smaller than that of glargine. The relatively large treatment effects in the present study are probably attributable to the higher starting HbA1c level, as it is generally acknowledged that the absolute reduction with treatment is proportional to the starting value [19,20], as observed in our cohort. The switch from liraglutide to glargine led to an incremental improvement in HbA1c in the extension phase, demonstrating additional glucose-lowering efficacy with insulin over the GLP-1 receptor agonist; however, this improvement came with increased rates of weight gain and hypoglycaemia.

Insulin glargine and liraglutide were compared previously in subjects taking oral agents in the LEAD 5 trial [13]. In that study subjects with T2DM with starting HbA1c levels of ∼8.2% received full-dose liraglutide (1.8 mg/day), similar to the dose used in the present study, or titrated glargine. In contrast to the results of the present EAGLE study, liraglutide reduced HbA1c slightly, but significantly, more than glargine, and a greater percentage of subjects reached the target HbA1c of 7%. However, in Lead 5, the average dose of insulin was ∼50% of the dose used in the present study, and the mean fasting glucose was 7.4 mmol/L, ∼20% higher than the glargine-treated subjects in the present study. It is plausible that with more aggressive use of insulin, the two treatments in LEAD 5 would have been comparable as they were in EAGLE.

In addition to fasting glucose level, the mean daily glucose level based on the subject's monitoring, was also lower in the subjects treated with glargine than in those treated with liraglutide. This is compatible with a mechanism of action of basal insulin to control hepatic glucose production overnight and in the intermeal intervals [2,21]. Despite significantly higher fasting blood glucose levels in subjects treated with liraglutide, the changes in HbA1c were comparable, suggesting a greater effect of the GLP-1 receptor agonist on postprandial glucose. This effect has also been shown with the GLP-1 receptor agonists exenatide and lixisenatide, which delay gastric emptying as well as regulate islet hormone release, responses that are effective in maintaining glycaemia after eating [11,22,23]. One implication of these results is that basal insulin and GLP-1 receptor agonists are complementary and would be effective when used together, as recently shown in a trial comparing basal insulin plus lixisenatide with rapid-acting insulin in combination with basal insulin [24].

In general, participants tolerated their injectable therapies well over the 24 weeks of this trial. While TEAEs were reported in half the subjects taking glargine and two-thirds of those on liraglutide, serious adverse events occurred in only 2–3% of subjects. However, more of the subjects taking liraglutide (7%) than of those taking glargine (1%) withdrew from the trial because of treatment effects. In addition, two subjects taking liraglutide reported severe hypoglycaemia, whereas no severe hypoglycaemia was reported with glargine. Subjects

taking glargine had a mean increase of body weight of nearly 2 kg, similarly to other studies using a systematic titration approach [17]. Subjects taking liraglutide lost nearly 3 kg on average, consistent with a recent meta-analysis of weight loss with GLP-1 receptor agonists [25]. As expected, glargine use was associated with greater rates of hypoglycaemia, occurring at a ∼4-fold greater rate than in the liraglutide group. Despite use of sulphonylurea in the liraglutide arm by almost half of the subjects, rates of hypoglycaemia were less in the present EAGLE trial than in previous trials with this drug [13].

The present study has some limitations that should be considered. As glargine and liraglutide have different titration requirements the study was open-label and thus subject to investigator/participant bias more than are blinded trials. Multicentre studies involving insulin titration, even with prescribed schedules, have more site-to-site variability than those using fixed-drug dosing. The duration of the study was relatively short at 6 months, although this was in keeping with similar trials comparing diabetes drugs [13,16,17,26]. The short study duration may have prevented some subjects in the glargine group from reaching the target HbA1c. Moreover, we cannot comment on the durability of treatment responses and how these might differ between the agents over several years of treatment. Finally, as only clinical endpoints were used, any conclusions about the mechanism of action of glargine and liraglutide in these subjects with diabetes is only conjectural.

In summary, the EAGLE trial shows that injectable therapies are effective and well tolerated in subjects with poorly controlled T2DM. In this group of subjects with diabetes and poor glycaemic control, typical of patients in whom diabetes therapy is intensified and injectable therapy frequently considered, both glargine and liraglutide caused large reductions in HbA1c levels, such that almost half of the subjects reached a glycaemic target of 7%. These findings support the use of injectable therapies in subjects with HbA1c values 1.5–2% above goal. The choice between basal insulin and a GLP-1 receptor agonist will depend on the potential adverse effects in a given patient as well as on the cost and availability of medication.

Acknowledgements

Conflict of Interest

D. D.'A. has served as a consultant to Janssen, Eli Lilly, Merck, Novo Nordisk, Roche, and Zealand and has received research grants from MannKind, Ethicon Endosurgery and Procter and Gamble; H.-U. H. has served on the advisory panel for Boehringer Ingelheim GmbH & Co., KG, Daiichi-Sankyo, Inc., Roche Pharmaceuticals and Sanofi. B. C. has served as a consultant to AstraZeneca/Bristol-Myers Squibb, Boehringer Ingelheim GmbH & Co., KG, Eli Lilly and Company,

GlaxoSmithKline, Janssen Biotech, Inc., Merck Sharp & Dohme, Novartis Pharmaceuticals Corporation, Novo Nordisk A/S, Roche Pharmaceuticals, Sanofi, and Takeda Global Research & Development Center, Inc., and on the speaker's bureau for AstraZeneca/Bristol-Myers Squibb, Boehringer Ingelheim GmbH & Co., KG, Eli Lilly and Company, Glaxo-SmithKline, Janssen Biotech, Merck Sharp & Dohme, Novartis Pharmaceuticals Corporation, Novo Nordisk A/S, Roche Pharmaceuticals, Sanofi, and Takeda Global Research & Development Center, Inc.; P. d. P.-V. has served on scientific advisory boards and received honoraria or consulting fees or grants/research support from insulin and GLP-1 receptor agonist manufacturers, Eli Lilly, AstraZeneca and Sanofi; C. C., M.-P. D., M. V. and V. P. are employees of Sanofi; H. Y.-J. has received honoraria for consulting and speaking for Boehringer Ingelheim GmbH & Co., Eli Lilly and Company, Merck Sharp & Dohme and Sanofi.

D. D. contributed to the data acquisition, data analysis/interpretation, writing and critical revision of the manuscript. H. H. contributed to the critical revision of the manuscript. B. C. contributed to the concept/design, data analysis/interpretation, writing and critical revision of the manuscript. P. d. P.-V. contributed to the concept/design, data acquisition, data analysis/interpretation, writing and critical revision of the manuscript. C. C. contributed to data analysis/interpretation and critical revision of the manuscript. M.-P. D. contributed to the concept/design, data analysis/interpretation and critical revision of the manuscript. M. V. contributed to data analysis/interpretation, writing and critical revision of the manuscript. V. P. contributed to the concept/design, data acquisition, data analysis/interpretation, writing and critical revision of the manuscript. H. Y.-J. contributed to data analysis/interpretation and critical revision of the manuscript.

Supporting Information

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

Figure S1. Disposition of subjects in the comparative study.

Table S1. Number of randomized subjects by country: comparative study.

Table S2. Insulin glargine dose titration.

Table S3. Baseline, endpoint and change from baseline in glycated haemoglobin (HbA1c) by quartiles of baseline HbA1c: comparative study.

Table S4. Serious treatment-emergent adverse events in the safety population: comparative study.

Table S5. Number (%) of subjects experiencing treatment-emergent adverse events leading to permanent treatment discontinuation: comparative study, safety population.

Table S6. Baseline, endpoint and change from baseline in blood pressure, heart rate and lipid profiles: comparative study, safety population.

Table S7. Demographic and baseline characteristics: modified intent-to-treat population, extension phase.

Table S8. Treatment-emergent adverse events – safety population, extension phase.

Appendix S1. EAGLE Study Group.

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