


ORIGINAL ARTICLE

Liraglutide as add-on to sodium-glucose co-transporter-2 inhibitors in patients with inadequately controlled type 2 diabetes: LIRA-ADD2SGLT2i, a 26-week, randomized, double-blind, placebo-controlled trial

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Abstract

Aim: To compare the effect of liraglutide or placebo added on to sodium-glucose co-transporter-2 inhibitor (SGLT2i) ± metformin on glycaemic control in patients with type 2 diabetes.

Materials and Methods: Patients with type 2 diabetes on a stable SGLT2i dose ± metformin (with HbA1c 7.0%–9.5% and body mass index [BMI] ≥20 kg/m²) were randomized 2:1 to add-on liraglutide 1.8 mg/day or placebo in this parallel, double-blind, multinational trial. Primary and confirmatory secondary endpoints were changes in HbA1c and body weight from baseline to week 26, respectively. The proportions of patients achieving HbA1c (<7.0%) targets and safety events after week 26 were also assessed.

Results: Of 303 patients randomized (one in error), 280 completed treatment. Mean changes in HbA1c from baseline to week 26 with liraglutide (n = 202) and placebo (n = 100) were −0.98% and −0.30%, respectively (estimated treatment difference [ETD]: −0.68% [95% CI: −0.89, −0.48]; *P* < 0.001). Mean body weight changes from baseline were −2.81 versus −1.99 kg, respectively (ETD: −0.82 kg [95% CI: −1.73, 0.09]; *P* = 0.077); 51.8% of liraglutide-treated patients achieved HbA1c <7.0% versus 23.2% receiving placebo (odds ratio: 5.1 [95% CI: 2.67, 9.87]; *P* < 0.001). More patients treated with liraglutide reported ≥1 treatment-emergent adverse events (66.3%) versus placebo (47.0%).

Conclusions: Liraglutide significantly improved glycaemic control compared with placebo in patients with type 2 diabetes, insufficiently controlled with SGLT2is with/without metformin, with no unexpected safety findings.

KEYWORDS

glucagon-like peptide-1, liraglutide, randomized trial, sodium-glucose co-transporter-2 inhibitor.

1 | INTRODUCTION

Because type 2 diabetes (T2D) is a progressive disease, the majority of patients will require intensification of antihyperglycaemic treatments over time in order to attain and maintain glycaemic control.¹ The American Diabetes Association (ADA),² American Association of Clinical Endocrinologists (AACE)³ and other international associations¹ recommend combining antihyperglycaemic agents with complementary mechanisms of action when glucose-lowering intensification is needed.

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose co-transporter-2 inhibitors (SGLT2is) are drug classes that have been proven separately to improve glycaemic control.^{1,2,4} Both classes are also associated with additional benefits, including reductions in blood pressure and body weight, low hypoglycaemia rates and a favourable safety profile in patients with T2D.^{1,2} The ADA/European Association for the Study of Diabetes (EASD) recommend GLP-1RAs as the preferred initial injectable therapy for patients with T2D and inadequately controlled HbA1c.¹ This drug class has a glucose-dependent stimulatory effect on insulin secretion and an inhibitory effect on glucagon secretion from the pancreatic islets.^{1,5} SGLT2is have an insulin-independent mode of action, lowering blood glucose through increased urinary glucose excretion.⁶ Despite different mechanisms of action, both GLP-1RAs (liraglutide, semaglutide, albiglutide and dulaglutide) and SGLT2is (dapagliflozin, empagliflozin and canagliflozin), administered separately, have been shown to reduce the time to various cardiovascular (CV) events (eg, CV death, non-fatal myocardial infarction, non-fatal stroke or hospitalization for heart failure [HF]) versus placebo in patients with T2D and at high risk of CV events.^{2,7-13} Also, other differences between the classes are evident. For example, the risk of worsening HF or death from CV causes was lower with dapagliflozin compared with placebo, in patients with T2D, HF and reduced ejection fraction.¹⁴ Because of these mechanisms of action and other differences, the combined use of GLP-1RAs and SGLT2is is recommended by treatment guidelines.²

To date, however, randomized controlled trial data on the combined use of these two drug classes have been limited. Just three trials, AWARD-10, DURATION 8 and SUSTAIN 9, have reported improvements in glycaemic measures and CV risk factors with combined GLP-1RA and SGLT2i treatment.¹⁵⁻¹⁷

Randomized trials of liraglutide, as a monotherapy and combined with other therapies (including metformin, sulphonylureas, thiazolidinediones and basal insulin), have shown its efficacy and safety,¹⁸⁻²⁰ as have studies in patients with T2D and either moderate or severe renal impairment²¹ or increased CV risk.¹⁰

The LIRA-ADD2SGLT2i trial assessed the effect on glycaemic control of adding liraglutide 1.8 mg/day versus placebo to SGLT2i ± metformin in patients with inadequately controlled glycaemia.

2 | MATERIALS AND METHODS

2.1 | Trial design

This was a 26-week, randomized (2:1 liraglutide or placebo), double-blind, placebo-controlled, parallel-arm, multicentre, multinational phase 3b trial (ClinicalTrials.gov NCT02964247) at 74 sites in Brazil, India, Israel, Mexico, the Russian Federation, United Arab Emirates and the United States. It was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practices Guidelines. The protocol was approved by local institutional review boards and ethical committees. All participants provided written informed consent.

2.2 | Participants

Eligible adults (aged ≥18 years) with T2D and HbA1c 7.0%–9.5%, body mass index (BMI) ≥20 kg/m² and on a stable dose of an SGLT2i for at least 90 days as monotherapy or combined with a stable metformin dose (≥1500 mg or maximum tolerated dose) were included in the trial. Exclusion criteria included a history of diabetic ketoacidosis (DKA) while being treated with SGLT2is, family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma, history of acute or chronic pancreatitis and estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m².

2.3 | Randomization and masking

Participants were randomized (2:1) to be treated with a once-daily subcutaneous injection of liraglutide 1.8 mg/day or placebo, stratified by metformin use at baseline (yes/no). Liraglutide and placebo were provided in identical prefilled pen injectors. Randomization was completed using an interactive web response system. Investigators and trial staff remained blinded to the treatment groups until after database lock.

2.4 | Procedures

The trial consisted of a 2-week screening period, 26-week treatment period and a 1-week follow-up period. The trial treatment regimen consisted of dose escalation for liraglutide and placebo (for further details see the Supplementary Appendix in the supporting information). Any approved dose of commercially available SGLT2i (canagliflozin, dapagliflozin or empagliflozin) was allowed as pretrial background therapy, either as monotherapy or combined with metformin, including a fixed-dose combination of SGLT2i + metformin. Unless antihyperglycaemic rescue medication was required or safety concerns arose, background medication was maintained at the same dose level as at trial entry throughout the trial.

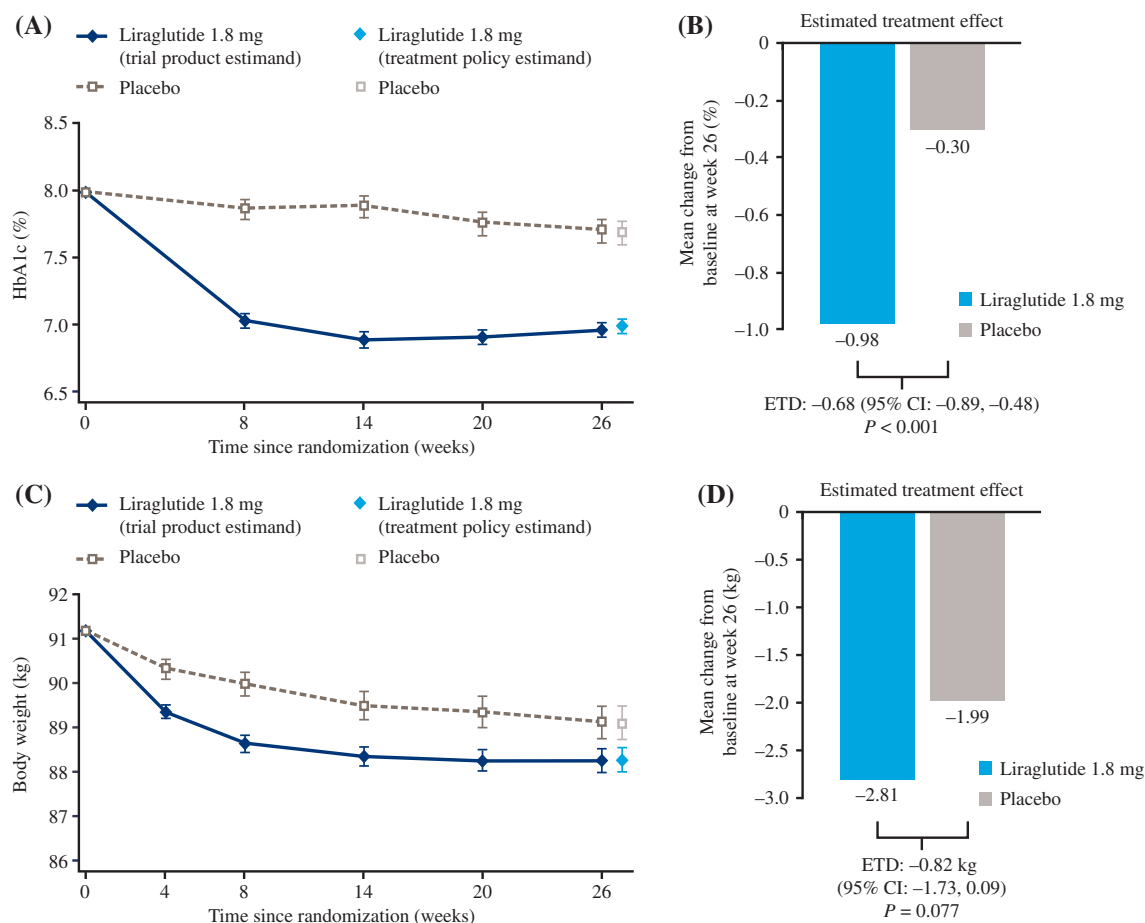


FIGURE 1 Change from baseline in HbA1c and body weight at week 26. (A) Mean HbA1c levels over 26 weeks, (B) HbA1c treatment effect at week 26 based on the in-trial observation period, (C) mean body weight over 26 weeks, and (D) body weight treatment effect at week 26 based on the in-trial observation period. Estimated treatment effect was calculated using treatment policy estimands with a pattern mixture model (PMM), which were based on the in-trial observation period, including the effect of any rescue medication, regardless of whether patients prematurely discontinued trial product. Trial product estimands calculated using mixed model of repeated measurements (MMRMs) were based on the on-treatment without rescue medication observation period. Error bars represent the standard error. ETD, estimated treatment difference

During the treatment period, fasting plasma glucose-based rescue medication criteria²² were applied to ensure acceptable glycaemic control in both treatment groups (for further details on rescue medication, refer to the Supplementary Appendix). All efforts were made to ensure that participants completed all scheduled visits and stayed in the trial regardless of non-adherence to randomized treatment, visit schedule or assessments, or the requirement for rescue therapy. For further details on trial procedures, refer to the Supplementary Appendix. For protocol amendments after trial commencement, see Table S1.

2.5 | Outcomes

The primary objective was to compare the effect of liraglutide 1.8 mg/day versus placebo as add-on to an SGLT2i ± metformin on glycaemic control in patients with T2D. The primary endpoint was change in HbA1c from baseline to 26 weeks. The confirmatory secondary endpoint was change in body weight from baseline to week

26. Additional supportive secondary endpoints were the percentage of patients achieving HbA1c and body weight treatment targets, and composite endpoints at week 26 (HbA1c <7.0%, HbA1c ≤6.5%, HbA1c <7.0% without severe or blood glucose-confirmed symptomatic hypoglycaemic episodes or weight gain, HbA1c reduction of ≥1.0% with body weight loss of ≥3%).

The following were also measured: change from baseline to week 26 in fasting plasma glucose and self-measured blood glucose (SMBG) seven-point profile (mean seven-point profile and mean postprandial increments [over all meals]). CV risk factors measured were fasting blood lipids, BMI, waist circumference, systolic and diastolic blood pressure (SBP and DBP, respectively) and pulse. Finally, from the blood samples which were collected, fasting hormones (glucagon, C-peptide and insulin) were measured at weeks 14 and 26 (Supplementary Appendix). Adverse events (AEs), hypoglycaemic episodes, laboratory variables, vital signs and electrocardiograms were assessed for safety (further details on safety assessments/definitions are provided in the Supplementary Appendix).

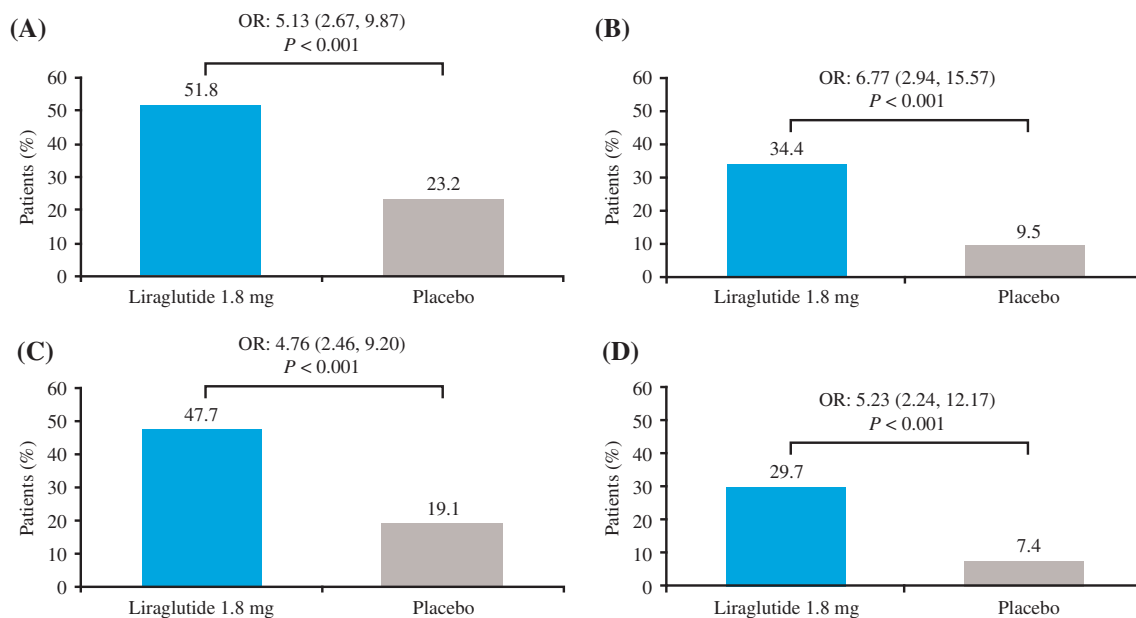


FIGURE 2 Proportion of patients reaching HbA1c targets and composite endpoints from baseline to 26 weeks (based on the in-trial observation period)*. (A) Patients reaching an HbA1c target of <7.0%, (B) patients reaching an HbA1c target of ≤6.5%, (C) patients reaching an HbA1c target of <7.0% without severe or blood glucose (BG)-confirmed symptomatic hypoglycaemia or body weight gain, and (D) HbA1c reduction of ≥1.0% with body weight loss ≥3%. *Treatment policy estimand using the in-trial observation period including the effect of any rescue medication and regardless of whether subjects prematurely discontinued trial product. Hypoglycaemia classifications: severe or BG-confirmed symptomatic: either severe according to the American Diabetes Association (ADA) definition (requiring assistance from another person)³³ or an episode accompanied by a plasma BG value of <3.1 mmol/L (56 mg/dL), with symptoms consistent with hypoglycaemia. n, number of patients experiencing at least one event; OR, odds ratio (with 95% confidence interval); %, percentage of patients experiencing at least one event

2.6 | Statistical analyses

To confirm superiority of liraglutide over placebo as add-on to SGLT2is, the sample size was calculated to ensure a statistical power of at least 90%. Based on previous trials in the liraglutide phase 3a clinical development programme, it was assumed that 25% of patients would discontinue trial treatment, initiate rescue medication or not complete all visits. A treatment difference of −0.5% and standard deviation (SD) of 1.1% for HbA1c, and of −2.0 kg and SD of 4.0 kg for body weight, were assumed. Based on these assumptions, allocating 202 patients to the liraglutide group and 101 to the placebo group would provide the required statistical power to confirm superiority in HbA1c and body weight change from baseline to week 26 for liraglutide versus placebo at a nominal two-sided 5% significance level.

Two distinct statistical approaches were applied (mandated by the US Food and Drug Administration for diabetes studies²³ and used elsewhere).²⁴ The first approach was that of the treatment policy estimand, which evaluated the average treatment effect in all randomized patients, regardless of adherence to treatment, or use of rescue glucose-lowering medication. The statistical analysis for this was a pattern mixture model. In this, missing data at week 26 were imputed 1000 times; for each of these datasets, the change in HbA1c from baseline to week 26 was analysed using an analysis of covariance (ANCOVA) with treatment, country and the metformin use at baseline

stratification factor as categorical fixed effects, and baseline HbA1c as covariate. The results from the imputed datasets were combined using Rubin's rule to draw inference. A hierarchical testing procedure was predefined to control the overall type I error, first testing for superiority in HbA1c, and second testing for superiority in body weight, both at a nominal two-sided 5% significance level.

The second statistical approach used was the trial product estimand, which evaluated the average treatment effect for all randomized patients, under the assumption that all remained on trial product for the entire trial duration, without using glucose-lowering treatment. It was estimated using a mixed model for repeated measurements for on-treatment without rescue medication data. The model included treatment, country and the stratification factor (metformin yes/no) as categorical fixed effects, and baseline HbA1c as a covariate, all nested within visit.

Sensitivity analyses for both approaches were conducted to assess the assumptions related to missing data and evaluate the robustness of the results of the confirmatory analyses. Throughout, treatment policy estimands have been presented for most endpoints. For fasting hormones, however, the trial product estimands have been reported in the main text, as these were more appropriate when exploring the endocrine mechanisms of the combined use of liraglutide and SGLT2is. For the majority of endpoints, the alternative estimands have been included in the Supplementary Appendix.

The percentages of patients achieving HbA1c targets were analysed using a logistic regression model with treatment, stratification factor and country as categorical fixed effects, and baseline response as covariate for the 1000 imputed complete datasets. Response status was determined from the imputed continuous responses, with inference drawn using Rubin's rule. Participant demographics and safety events (including hypoglycaemic episodes) were analysed descriptively only. Statistical analyses were performed with SAS version 9.4.

3 | RESULTS

Overall, 412 patients were screened, 303 randomized (but one in error) and 298 (98.3%) completed the trial (remained in the trial until

its end, but not necessarily taking trial treatment: 98.5% with liraglutide and 98.0% with placebo) between 3 March, 2017 and 8 May, 2018. Of those randomized correctly, 280 patients (92.4%) completed treatment (were taking trial treatment at trial end: 92.1% with liraglutide, 93.0% with placebo; Figure S1). Baseline characteristics were balanced between treatment groups (Table 1). Approximately 60% of the population were men, the mean age was 55.2 years, mean HbA1c was 8.0%, and mean BMI and body weight were 32.2 and 91.1 kg, respectively. The mean reported diabetes duration was 9.9 years (Table 1).

The majority of patients were taking metformin at baseline (94.1% in the liraglutide and 95.0% in the placebo group; Table 1). Patients were required to have been on an SGLT2i for ≥ 90 days prior to screening; the proportions of patients receiving SGLT-2i for < 6 or ≥ 6 months were balanced between the treatment groups for each

TABLE 1 Baseline characteristics

	Liraglutide 1.8 mg (N = 203)	Placebo (N = 100)	Total (N = 303)
Mean (SD, unless otherwise stated)			
Sex, n (% males)	125 (62)	58 (58)	183 (60)
Age, years	54.7 (10.1)	56.0 (9.9)	55.2 (10.0)
Race, n (%)			
White	131 (64.5)	59 (59.0)	190 (62.7)
Black or African American	12 (5.9)	5 (5.0)	17 (5.6)
Asian	38 (18.7)	15 (15.0)	53 (17.5)
Other ^a	22 (10.8)	21 (21.0)	43 (14.2)
Diabetes duration, years	10.1 (7.2)	9.6 (6.7)	9.9 (7.0)
HbA1c, %	8.0 (0.7)	8.0 (0.6)	8.0 (0.7)
HbA1c, n (%)			
<8.5%	152 (74.9)	79 (79.0)	231 (76.2)
$\geq 8.5\%$	51 (25.1)	21 (21.0)	72 (23.8)
FPG, mg/dL	160.7 (41.7)	159.1 (46.3)	160.2 (43.2)
Body weight, kg	91.0 (21.0)	91.4 (21.4)	91.1 (21.1)
BMI, kg/m ²	32.0 (6.0)	32.6 (6.5)	32.2 (6.1)
BMI, kg/m ² , n (%)			
<25	13 (6.4)	14 (14.0)	27 (8.9)
25 to <30	72 (35.5)	22 (22.0)	94 (31.0)
30 to <35	64 (31.5)	34 (34.0)	98 (32.3)
35 to <40	34 (16.7)	20 (20.0)	54 (17.8)
≥ 40	20 (9.9)	10 (10.0)	30 (9.9)
SBP, mmHg	127.5 (12.7)	128.5 (14.4)	127.8 (13.3)
DBP, mmHg	79.2 (9.0)	79.3 (8.9)	79.3 (8.9)
SGLT2i, n (%)			
Dapagliflozin	96 (47.3)	54 (54.0)	150 (49.5)
Empagliflozin	55 (27.1)	23 (23.0)	78 (25.7)
Canagliflozin	52 (25.6)	23 (23.0)	75 (24.8)
Metformin	191 (94.1)	95 (95.0)	286 (94.4)
eGFR, mL/min/1.73 m ² , n (%)			
Normal (≥ 90)	149 (73.4)	72 (72.0)	221 (72.9)
Mildly decreased (60 to <90)	53 (26.1)	28 (28.0)	81 (26.7)
UACR >30 mg/g, n (%)	51 (25.9)	18 (18.6)	69 (22.8)

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; SBP, systolic blood pressure; SGLT2i, sodium-glucose co-transporter-2 inhibitor; UACR, urinary albumin-to-creatinine ratio.

^aOther includes American Indian or Alaska Native, Native Hawaiian, or Other Pacific Islander and others.

TABLE 2 Adverse events and hypoglycaemic episodes

	Liraglutide 1.8 mg (N = 202)	Placebo (N = 100)
	n (%)	n (%)
Deaths	0 (0.0)	0 (0.0)
Serious adverse events ^a	5 (2.5)	1 (1.0)
Treatment-emergent adverse events ^b	134 (66.3)	47 (47.0)
Severe	6 (3.0)	2 (2.0)
Possibly or probably related	102 (50.5)	18 (18.0)
Trial treatment discontinuation because of adverse events	8 (4.0)	2 (2.0)
Adverse events (≥5%)		
Nausea	53 (26.2)	6 (6.0)
Vomiting	17 (8.4)	2 (2.0)
Diarrhoea	19 (9.4)	3 (3.0)
Constipation	18 (8.9)	0 (0.0)
Decreased appetite	19 (9.4)	0 (0.0)
Enzymatic adverse events		
Lipase	2 (1.0)	0 (0.0)
Pancreatic enzymes increase	1 (0.5)	0 (0.0)
Hypoglycaemic episodes		
All episodes	18 (8.9)	8 (8.0)
Severe or BG-confirmed symptomatic ^c	0 (0.0)	3 (3.0) ^e
ADA classification ^d		
Severe	0 (0.0)	0 (0.0)
Documented symptomatic	6 (3.0)	7 (7.0)
Asymptomatic	9 (4.5)	2 (2.0)
Probable symptomatic	2 (1.0)	0 (0.0)
Pseudo-hypoglycaemia	4 (2.0)	0 (0.0)
ADA unclassified	0 (0.0)	0 (0.0)

Abbreviations: ADA, American Diabetes Association; BG, blood glucose; n, number of patients experiencing at least one event; %, percentage of patients experiencing at least one event; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

^aOne serious adverse event was judged by the investigator as possibly or probably related to trial product (the event of cholecystitis in the liraglutide group), which led to premature trial product discontinuation for the remainder of the trial. The case had resolved by the end of the trial.

^bNo adverse events of interest associated with SGLT2is (including diabetic foot ulcer, lower limb amputation or diabetic ketoacidosis) were reported. No cases of acute pancreatic or medullary thyroid cancer were reported.

^cSevere or BG-confirmed symptomatic: either severe according to ADA^d (requiring assistance from another person) or an episode accompanied by a plasma BG value <3.1 mmol/L (56 mg/dL), with symptoms consistent with hypoglycaemia.

^dADA Workgroup on Hypoglycemia. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia.³³

^eOne patient was on rescue medication with sulphonylureas.

SGLT2i (Table S2). At baseline, 49.5% of patients were taking dapagliflozin, 25.7% were taking empagliflozin and 24.8% were taking canagliflozin (Table 1). Of those taking dapagliflozin, 92.0% were

taking the highest dose available. Of those taking empagliflozin and canagliflozin, approximately half were taking the highest dose (43.6% with empagliflozin and 53.3% with canagliflozin); these percentages were balanced between the treatment groups. Throughout the trial, 12 patients were not uptitrated to the highest 1.8 mg daily liraglutide dose, and continued on 1.2 mg.

The mean HbA1c change from baseline at week 26 (primary endpoint) was -0.98% in those treated with liraglutide + SGLT2i compared with -0.30% for placebo + SGLT2i (estimated treatment difference [ETD], adjusted for baseline values: -0.68% [95% CI: $-0.89, -0.48$; $P < 0.001$]; Figure 1A,B and Table S3). Sensitivity analyses, involving different imputation models to account for missing data, showed that these results were robust (Figure S2).

Body weight decreased in both treatment groups at week 26 although the difference between the groups was not statistically significant. The estimated mean body weight change from baseline to week 26 was -2.81 kg in the liraglutide group versus -1.99 kg in the placebo group (ETD adjusted for baseline values: -0.82 kg [95% CI: $-1.73, 0.09$; $P = 0.077$]; Figure 1C,D and Table S3). In both treatment groups, body weight decreases were observed in patients with baseline HbA1c <8.0% or ≥8.0%, and in patients with baseline BMI <30 kg/m² and ≥30 kg/m², with no evidence of interaction (Table S4).

In the liraglutide group, 51.8% of patients achieved HbA1c <7.0% versus 23.2% in the placebo group (odds ratio: 5.1 [95% CI: 2.67, 9.87; $P < 0.001$]; Figure 2A), while 34.4% of patients achieved HbA1c ≤6.5% with liraglutide versus 9.5% with placebo (Figure 2B). When composite endpoints of HbA1c without hypoglycaemia or with weight loss/no gain were analysed, similar results were seen in favour of liraglutide over placebo (Figure 2C,D and Table S5).

Liraglutide showed a statistically significant greater reduction in fasting plasma glucose compared with placebo, with an ETD of -0.80 mmol/L (95% CI: $-1.26, -0.35$; $P < 0.001$; Table S3). Liraglutide also reduced the seven-point SMBG mean profile change from baseline at 26 weeks compared with placebo (ETD -0.71 mmol/L [95% CI: $-1.13, -0.29$; $P < 0.001$]; Figure S3 and Table S3).

Comparing ratios to baseline after 26 weeks, adding liraglutide to SGLT2i ± metformin resulted in statistically significant reductions versus placebo in total cholesterol, very low-density lipoprotein cholesterol, triglycerides and free fatty acids (Figure S4A-D). However, no statistically significant differences in HDL or LDL cholesterol were observed between the treatment groups at week 26 (Figure S4E-F).

From baseline to week 26, there was no significant treatment difference in BMI between patients in the liraglutide and placebo groups (ETD: -0.33 kg/m² [95% CI: $-0.65, 0.00$; $P = 0.052$]; Table S3). Patients in the liraglutide group showed greater waist circumference reduction than those in the placebo group (ETD: -1.96 cm [95% CI: $-3.86; -0.07$; $P = 0.042$]; Table S3). No differences in SBP and DBP were observed between the liraglutide and placebo groups (ETD: 0.25 mmHg [95% CI: $-2.51, 3.00$; $P = 0.861$] and ETD: 0.12 mmHg [95% CI: $-1.65, 1.90$; $P = 0.894$], respectively; Table S3). Mean pulse rate increased with liraglutide by 4.4 beats per minute from baseline (SD 10.2), but decreased with placebo by 1.4 beats per minute (SD 8.6).

In both treatment groups, fasting glucagon levels decreased from baseline to end of treatment, with the greatest declines observed between baseline and week 14. Levels of fasting glucagon were found to be slightly lower in the liraglutide versus placebo group at both weeks 14 and 26; however, the difference was not significant (ETR: 0.96 [95% CI: 0.82, 1.12; $P = 0.579$]; Table S6). Fasting insulin and C-peptide increased from baseline to weeks 14 and 26, and were statistically significantly greater with liraglutide versus placebo (ETR: 1.20 [95% CI: 1.07, 1.35; $P = 0.002$] and ETR: 1.15 [95% CI: 1.07, 1.25; $P < 0.001$], respectively; Table S6).

A higher percentage of patients in the liraglutide group reported one or more treatment-emergent AEs than in the placebo group (66.3% vs. 47.0%). The percentage of patients reporting serious AEs was low in both groups (liraglutide 2.5% vs. placebo 1.0%; Table 2). Nausea was the most frequent AE, occurring in 26.2% (liraglutide group) and 6.0% (placebo group) of patients (Table 2), and generally had early onset (initial 4 weeks) and was transient. The proportion of patients experiencing possible or probable treatment-related AEs, and who discontinued treatment because of AEs, was higher in the liraglutide group than in the placebo group, and both were mainly because of gastrointestinal AEs (Table 2). Incidences of hypoglycaemia were 8.9% with liraglutide versus 8.0% with placebo; none were severe according to the ADA definition (requiring assistance from another person; Table 2). There was one event of acute kidney injury in the placebo group. No deaths occurred in either group, and there were no reports of hypovolemia, acute renal failure, DKA, diabetic foot ulcers or amputations with liraglutide combined with SGLT2is. Treatment with liraglutide or placebo did not have any impact on eGFR or urinary albumin-to-creatinine ratio (Supplementary Appendix). No clinically relevant changes in other safety variables (laboratory assessments, physical examinations and electrocardiogram readings) were observed.

4 | DISCUSSION

The LIRA-ADD2SGLT2i trial showed the superiority of liraglutide 1.8 mg/day over placebo in improving glycaemic control in patients with T2D and inadequately controlled HbA1c despite treatment with SGLT2i ± metformin. Body weight, the confirmatory secondary endpoint, was reduced in both treatment groups, and the small, numerically greater reduction seen with liraglutide versus placebo was not statistically significant. According to the ADA, a reasonable HbA1c goal for many non-pregnant adults is $<7.0\%$.⁴ Thus it is clinically important that in this trial more than half of the patients in the liraglutide group achieved a target of HbA1c $<7.0\%$ compared with less than a quarter of patients in the placebo group. Additionally, one third of patients achieved the more stringent HbA1c $\leq 6.5\%$ with liraglutide versus less than 10% with placebo. This glycaemic efficacy was also evident in the proportion of patients achieving composite endpoints, eg, good glycaemic control without severe hypoglycaemia or weight gain that was achieved in a greater percentage of patients on liraglutide (47.7%) versus placebo (19.1%). Other variables such as

SBP and LDL cholesterol were not reduced significantly from baseline when comparing liraglutide with placebo; however, triglycerides were reduced in the liraglutide group. Importantly, these glycaemic and other benefits were achieved without identifying any new safety issues, with safety findings in this trial consistent with the established safety profile of each individual therapy,²⁵⁻²⁸ and were in accordance with the two previous combination trials (AWARD-10 and SUSTAIN 9).^{15,17}

The addition of liraglutide to an existing SGLT2i treatment did not result in statistically significant reductions in body weight compared with placebo. In previous trials where liraglutide was used combined with more than one oral antihyperglycaemic agent (LEAD-4, -5 and -6), body weight was reduced by 1.8–3.2 kg over 26 weeks in the liraglutide 1.8 mg/day groups,^{18,20} similar in magnitude to that reported within this trial in the liraglutide group. However, in LIRA-ADD2SGLT2i, the patients in the placebo group also had a substantial reduction in body weight. This unexpected result may have been because of the trial effect, as placebo-treated patients were less likely to achieve a similar level of glycaemic control compared with the liraglutide group, and therefore may have received greater encouragement from the investigator and/or study coordinators to better adhere to diet and exercise throughout the 26-week trial. In various SGLT2i phase 3a trials, body weight continued to decrease over the first 6 months,²⁹ while HbA1c reduction plateaued after 3 months.³⁰ In this trial, the duration and dose of an SGLT2i at enrolment were balanced between the treatment groups, and therefore are unlikely to explain this unexpected weight loss in the placebo group.

In previous T2D trials combining an SGLT2i with a GLP-1RA, diverse body weight results have been found. In the AWARD-10 trial, dulaglutide 0.75 mg did not show a significant reduction in body weight versus placebo, while the highest dose (1.5 mg) showed a modest treatment difference of -0.9 kg between dulaglutide and placebo and reached statistical significance.¹⁵ This treatment difference was very similar to the non-significant -0.82 kg greater weight loss with liraglutide in this trial. Published results from SUSTAIN 9 showed a profound body weight reduction with semaglutide 1.0 mg added to an SGLT2i, with a treatment difference of -3.8 kg favouring semaglutide.¹⁷ In DURATION 8, where exenatide and dapagliflozin were initiated simultaneously, a greater reduction of body weight was observed in the combination group compared with those who received either of the two components as monotherapy (ETD -1.87 kg vs. exenatide alone [$P < 0.001$] and -1.22 kg vs. dapagliflozin alone [$P = 0.002$]).¹⁶ In DURATION 8, no placebo group was investigated.

Treatment with SGLT2is might be associated with elevations in plasma glucagon concentrations that could sustain endogenous glucose production, offsetting some of the glucose-lowering capacity of these agents.³¹ In the current trial, fasting glucagon declined in both treatment groups, which was surprising to observe in the placebo group; however, different metabolic responses have been reported dependent on acute or chronic intervention with SGLT2is.³² These results are also comparable with AWARD-10, where the placebo group also showed a small decrease in fasting glucagon levels.¹⁵ It might have been more appropriate to have used postprandial glucagon levels to assess the impact of liraglutide and SGLT2is on glucagon

homeostasis. However, this would have been more challenging to implement in a large trial.

The safety profile shown for liraglutide added to SGLT2is was consistent with that seen in previous trials assessing liraglutide as monotherapy or combined with other antihyperglycaemic agents.¹⁸⁻²⁰ During the trial, very few patients discontinued treatment overall or because of AEs, emphasizing that this combination was well tolerated. Only one acute renal injury event was reported, which occurred in the placebo group.

A limitation of this trial was the inclusion criteria of HbA1c 7.0%–9.5%, which is narrower than that typically seen in clinical practice. Another limitation was that some patients (n = 12) were not uptitrated to the highest 1.8 mg liraglutide dose, but continued on 1.2 mg. These differences in product exposure may have limited the safety and tolerability results of the 1.8 mg/day dose and impacted the weight reduction obtained by patients. Furthermore, as a liraglutide-only group was not included, it remains unclear as to whether the combination of liraglutide + SGLT2is has an additive or synergistic effect on efficacy. The generalizability of these results to a real-world setting has yet to be explored.

In conclusion, the LIRA-ADD2SGLT2i trial showed that liraglutide improved glycaemic control in patients with T2D insufficiently controlled with SGLT2is ± metformin, with no unexpected safety findings. This combination is an efficacious option for patients who need to intensify glucose-lowering therapy.

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Parts of these results were presented at the ENDO 2019 conference, 23-26 March 2019, in New Orleans, LA, United States, and at the 55th EASD annual meeting, 16-20 September 2019, in Barcelona, Spain.

CONFLICT OF INTEREST

La.B. declares research support from Janssen, Lexicon, Merck, Novo Nordisk and Sanofi; speaker honoraria from Janssen, Novo Nordisk and Sanofi; consultant honoraria from AstraZeneca, Gilead, Janssen, Merck, Novo Nordisk and Sanofi. P.A.G.-H. declares research support and honoraria from Amgen, Eli Lilly and Novo Nordisk. S.M.J. declares research support, speaker honorarium and advisory board membership from TOTALL Diabetes Hormone Institute. O.M. declares speaker's bureau honoraria and advisory board membership from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk and Sanofi; speaker's bureau honorarium from

Bristol Myers Squibb. R.R. declares speaker's bureau membership from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp & Dohme, Novo Nordisk, Sanofi and Takeda; research support from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Novo Nordisk and Sanofi; consulting fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly and Sanofi. U.F., M.S.K. and M.S.P. are employees of Novo Nordisk. Li.B. and J.N. declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

La.B., P.A.G.-H., S.M.J., O.M., R.R., Li.B. and J.N. acquired data for the LIRA-ADD2SGLT2i trial. M.S.K. was responsible for the trial conduct. All authors interpreted the data. M.S.P. analysed the data. All authors reviewed and commented on several drafts of the manuscript and approved the final version for publication. La.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors had the final decision to submit for publication.

DATA SHARING

Individual participant data will be shared in datasets in an anonymized format, including datasets from Novo Nordisk-sponsored clinical research completed after 2001 for product indications approved in both the European Union (EU) and United States. The study protocol and redacted Clinical Trial Report (CTR) will be available according to Novo Nordisk data-sharing commitments. The data will be available permanently after research completion and approval of product and product use in both the EU and United States. Data will only be shared with bona fide researchers submitting a research proposal and requesting access to data, as approved by the Independent Review Board according to the IRB Charter. Data will be made available on a specialized Novo Nordisk Statistical Analysis System data platform.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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