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Efficacy of liraglutide added to sodium-glucose cotransporter-2 inhibitors in type 2 diabetes, stratified by baseline characteristics: Post-hoc analysis of LIRA-ADD2SGLT2i

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Abstract

Aims: The LIRA-ADD2SGLT2i trial demonstrated that liraglutide + sodium-glucose cotransporter-2 inhibitors (SGLT2is) ± metformin significantly improved glycaemic control (not body weight) versus placebo in adults with type 2 diabetes (T2D). This post-hoc analysis assessed whether baseline characteristics influenced these findings.

Materials and methods: LIRA-ADD2SGLT2i (NCT02964247) was a placebo-controlled, double-blind, multinational trial, wherein participants received liraglutide (≤1.8 mg/day) or placebo (randomized 2:1). Changes from baseline to week 26 in haemoglobin A1c (HbA1c), body weight and waist circumference stratified by HbA1c, body mass index (BMI), diabetes duration, duration of pre-trial SGLT2i use and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) were analysed. These five baseline characteristics were divided into tertiles, and the treatment effect was evaluated using the trial product estimand.

Results: Data from all 303 participants were analysed. There was a significant interaction between baseline HbA1c tertiles (7.0%-<7.6%; 7.6%-8.1%; ≥8.2%-9.5%) and glycaemic control at week 26 ($p_{[interaction]} = .011$), with the lowest HbA1c estimated treatment difference (95% confidence interval) observed in patients with lowest baseline HbA1c [−0.20% (−0.59, 0.19); −0.68% (−1.03, −0.33); −0.98% (−1.33, −0.64), respectively]. There were no significant interactions in glycaemic control across baseline BMI, diabetes duration, insulin resistance determined by HOMA-IR or SGLT2i use duration ($p_{[interaction]} > .05$, all). Across the five characteristics assessed, no significant interactions were found for body weight or waist circumference changes from baseline ($p_{[interaction]} > .05$, all).

Conclusion: For individuals with T2D and inadequate glycaemic control despite therapy with SGLT2is ± metformin, liraglutide 1.8 mg would provide an effective treatment intensification option, irrespective of HbA1c, BMI, diabetes duration, insulin resistance determined by HOMA-IR and SGLT2i use duration.

KEYWORDS
antidiabetic drug, GLP-1 analogue, glycaemic control, liraglutide, SGLT2 inhibitor, type 2 diabetes

1 | INTRODUCTION

Type 2 diabetes (T2D) is often a progressive disease, albeit not inevitable with use of lifestyle interventions of medical nutrition therapy (including low calorie diets) and appropriately prescribed physical activity.[1] Given the difficulties in dietary management,[1] individuals will also require antihyperglycaemic pharmacotherapy regimens, which can also delay progression of T2D and its complications. As the disease progresses, the majority of patients will require treatment intensification to manage hyperglycaemia. Over the last two decades, several classes of antihyperglycaemic agents have emerged and increased the options for dual or triple therapy for individuals with T2D.[2] In accordance with guidance provided by the American Diabetes Association,[3] European Association for the Study of Diabetes[2] and American Association of Clinical Endocrinologists,[4] clinicians should combine antihyperglycaemic agents with complementary mechanisms of action to enhance therapeutic efficacy and improve long-term patient outcomes.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) are two classes of antihyperglycaemic agents with different mechanisms of action. SGLT2is act independently of insulin, while GLP-1 RAs act in a glucose-dependent way and enhance insulin secretion and suppress inappropriately high glucagon secretion. For reducing body weight, GLP-1 RAs and SGLT-2is provide complementary mechanisms, with the former reducing appetite and calorie intake due to its effect on hypothalamic nuclei, while the latter promote caloric deficits due to glycosuria.[5] The weight reduction in patients with diabetes treated with SGLT2is is generally smaller than what would be expected based on the urinary loss of glucose, implying some degree of compensatory increase in caloric intake. Thus, combining SGLT2i therapy with a medication that reduces appetite via the central nervous system would seem potentially beneficial.[5] Both drug classes are associated with weight-lowering effects and a low risk of hypoglycaemia as well as having demonstrated benefits on cardiovascular outcomes.[6,7] Currently, only four randomized controlled trials (AWARD-10, DURATION 8, SUSTAIN 9 and LIRA-ADD2SGLT2i) have investigated glycaemic control with the combined use of GLP-1 RAs and SGLT2is.[8-11] Even though the trial designs differed, the results suggested multiple benefits with this combination therapy and all four trials achieved their primary objective by demonstrating a significant reduction in haemoglobin A1c (HbA1c) with the combined use of GLP-1 RAs and SGLT2is, compared with either their monocomponents or placebo.[8-11] In LIRA-ADD2SGLT2i, there were no statistically significant reductions with liraglutide versus placebo in body weight observed, contrary to what was shown in AWARD-10 (although the superiority of dulaglutide vs. placebo was not confirmed by hierarchical testing),[9] DURATION 8[8] and SUSTAIN 9.[10] This result was surprising, as previous studies have found that GLP-1 RAs and SGLT2is separately result in weight loss in adults with T2D,[12-15] and it was anticipated that the two different mechanisms would produce an additive or synergistic effect on weight loss in that trial.[16,17]

The objective of this post-hoc analysis was to identify whether particular baseline characteristics [HbA1c, body mass index (BMI), duration of diabetes, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), and/or duration of pre-trial SGLT2i use] influence the efficacy [HbA1c, weight reduction and waist circumference (WC) changes] of liraglutide 1.8 mg when added to SGLT2i ± metformin versus placebo.

2 | MATERIALS AND METHODS

2.1 | Trial design

The LIRA-ADD2SGLT2i trial (ClinicalTrials.gov NCT02964247) was a phase 3b, double-blind, placebo-controlled, parallel-arm, multicentre, multinational trial in adults with T2D.[11] Key inclusion criteria were adults (aged ≥18 years) with T2D, HbA1c 7.0%-9.5%, BMI ≥20 kg/m^2 and on a stable dose of SGLT2i for at least 90 days, alone or combined with a stable metformin dose. Exclusion criteria included a history of diabetic ketoacidosis while being treated with SGLT2is, history of acute or chronic pancreatitis, history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma and estimated glomerular filtration rate <60 mL/min/1.73 m^2 (due to the regulatory approvals in place for SGLT2is at the time of trial design). Participants were randomized 2:1 to receive a once-daily subcutaneous injection of liraglutide (up to 1.8 mg/day) or placebo. The LIRA-ADD2SGLT2i trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practices Guidelines, and all participants provided written informed consent.[11] Further information on the LIRA-ADD2SGLT2i trial design, including titration details, can be found in the primary manuscript.[11]

2.2 | Statistical analyses

This post-hoc analysis examined change from baseline to week 26 in HbA1c, body weight and WC, according to treatment arm, based on baseline HbA1c, BMI, HOMA-IR, duration of diabetes or duration of pre-trial SGLT2i use. The initial trial evaluated the effect of liraglutide versus placebo added to SGLT2i by using two estimands. The current analysis focused on the trial product estimand, which investigated the

treatment effect of those who remained on therapy and were not given rescue medication. Each of the five baseline characteristics of interest (HbA1c, BMI, diabetes duration, duration of pre-trial SGLT2i use and HOMA-IR) was divided into tertiles, which were then analysed for interactions as follows: a pattern mixture model of on-treatment observation period data with missing observations imputed 1000 times based on patients who remained on therapy and were not given rescue medication within each randomized treatment group was used; for each of the 1000 imputed data sets, the changes from baseline to week 26 were analysed using an analysis of covariance (ANCOVA) with treatment, country, stratification by baseline metformin use and subgroup variable with interaction treatment and subgroup categorical fixed effects and baseline body weight as covariate. Estimated treatment differences (ETDs) and confidence intervals (CIs) were combined using Rubin's formula.

In addition, a sensitivity analysis was performed using the treatment policy estimand, which evaluated the treatment effect regardless of trial product discontinuation and use of rescue medication. Scatterplots with Pearson correlation analyses were performed to investigate the relationship between baseline HbA1c and change in HbA1c from baseline to week 26, and between baseline BMI and change in body weight (using both estimands).

One patient included in the original analyses was subsequently identified as an outlier (due to an abnormal fluctuation in body weight of >10 kg between screening and randomization and again over a period of 4 weeks post-randomization). Further exploratory analyses of body weight by baseline characteristics were performed, excluding this outlier, for both of the estimands.

Statistical analyses were performed using SAS version 9.4.

3 | RESULTS

3.1 | Baseline characteristics

In LIRA-ADD2SGLT2i, 303 participants were randomized and 280 (92.4%) completed treatment (92.1% with liraglutide, 93.0% with placebo).[11] As per the inclusion criteria, all participants had used SGLT2is ≥90 days before baseline, resulting in the median duration of pre-trial SGLT2i use of 6.3 months.

At baseline, the majority of patients were taking dapagliflozin (49.5%), with others taking empagliflozin (25.7%) or canagliflozin (24.8%). In patients taking dapagliflozin, 92.0% were taking the highest available dose (10 mg). In patients treated with empagliflozin and canagliflozin, 43.6% and 53.3% were taking the highest dose (25 and 300 mg), respectively. Percentages were balanced between the treatment groups.[11] The mean BMI at baseline was 32.2 kg/m^2 [standard deviation (SD): 6.1], and mean ± SD HbA1c 8.0% ± 0.7%. Median duration of diabetes at baseline was 9.9 years (SD 7.0). Baseline characteristics were balanced across treatment groups. The total trial population was analysed and the tertile values were subsequently applied to the two treatment groups. This resulted in analysis subgroups of approximately the same ratio as the initial trial randomization ratio of 2:1, with some placebo subgroups having low patient numbers of 26 or 27 patients.

3.2 | Glycaemic control by baseline characteristics

Significantly greater reductions in HbA1c with liraglutide versus placebo, both added to SGLT2i ± metformin, occurred after 26 weeks in the overall population (ETD adjusted for baseline values: −0.74%; 95% CI: −0.94, −0.53; $p < .001$; trial product estimand).[11] Analysing the change in HbA1c at week 26 using tertiles showed that this reduction occurred irrespective of baseline BMI, duration of diabetes, duration of pre-trial SGLT2i use or insulin resistance as HOMA-IR (Table 1). However, baseline HbA1c showed a significant interaction between tertiles and the ETD at week 26. In the trial product estimand, the higher the baseline HbA1c, the greater the ETD versus placebo ($p = .011$; Table 1). In patients treated with placebo, the mean reduction in HbA1c was greater for those with a baseline HbA1c 7.0%-<7.6%, compared with other tertiles (Table 1). Although there was not a significant interaction between change in HbA1c and baseline duration of SGLT2i use in the trial product estimand analysis, there appeared to be a trend for a better response in the placebo group with a shorter duration of pre-trial SGLT2i use and a larger treatment difference favouring liraglutide with a longer duration of pre-trial SGLT2i use (Table 1).

A correlation analysis showed that patients with the highest baseline HbA1c achieved greatest reductions in HbA1c at week 26 in the liraglutide arm ($r = 0.39$), but in the placebo arm there was a marginal change in the amount of HbA1c reduction with increasing baseline HbA1c values ($r = -0.03$) (Figure 1). Similar findings were observed for the treatment policy estimand (Table S1 and Figure S1, Appendix S1).

3.3 | Changes in body weight by baseline characteristics

Body weight reductions were observed in both treatment groups at week 26 (Tables 2 and S2, Appendix S1). With the exclusion of the single outlier, there was a statistically significant difference between groups (ETD adjusted for baseline values: −0.89 kg; 95% CI: −1.77, −0.02; $p = .046$; trial product estimand; Table S2, Appendix S1). However, statistical significance was not achieved when data from all patients (including the outlier) were analysed (ETD adjusted for baseline values: −0.86 kg; 95% CI: −1.77, 0.04; $p = .06$; trial product estimand; Table 2).[11] There were no significant interactions among ETDs in body weight between treatment arms across any baseline characteristic assessed (Tables 2 and S2, Appendix S1). In the baseline HbA1c 7.0%-<7.6% tertile, the treatment effect was in favour of placebo (Tables 2 and S2, Appendix S1). In addition, in the placebo arm, a trend was observed for greater body weight reduction in the baseline HbA1c 7.0%-<7.6% tertile compared with two higher

TABLE 1 Treatment effect (trial product estimand) on change from baseline to week 26 in HbA1c by baseline characteristics when liraglutide 1.8 mg versus placebo was added to stable SGLT2i ± metformin therapy in patients with T2D

Baseline characteristic	Tertile [n (liraglutide 1.8 mg), n (placebo)]	Tertile cut-off values	Mean change in HbA1c at week 26 (%)		ETD (95% CI) at week 26 (%)	*p*-value
			Liraglutide 1.8 mg	Placebo		
Overall change in HbA1c[11]			−1.02	−0.28	−0.74 (−0.94, −0.53)	$p < .001$
Baseline HbA1c	T1 (65, 27)	7.0%-<7.6%	−1.11	−0.90	−0.20 (−0.59, 0.19)	$p_{[interaction]} = .011$
	T2 (63, 35)	7.6%-8.1%	−0.99	−0.31	−0.68 (−1.03, −0.33)	
	T3 (75, 38)	≥8.2%-9.5%	−1.01	−0.02	−0.98 (−1.33, −0.64)	
BMI	T1 (75, 26)	<28.6 kg/m^2	−1.08	−0.10	−0.97 (−1.36, −0.59)	NS, $p_{[interaction]} = .13$
	T2 (61, 40)	28.6-33.9 kg/m^2	−0.91	−0.48	−0.44 (−0.78, −0.09)	
	T3 (67, 34)	≥34.0 kg/m^2	−1.10	−0.40	−0.70 (−1.07, −0.33)	
Diabetes duration	T1 (66, 35)	<5.6 y	−1.07	−0.50	−0.57 (−0.94, −0.20)	NS, $p_{[interaction]} = .69$
	T2 (69, 33)	5.6-11.6 y	−1.12	−0.44	−0.69 (−1.04, −0.33)	
	T3 (68, 32)	≥11.7 y	−0.90	−0.11	−0.80 (−1.16, −0.44)	
Duration of pre-trial SGLT2i use	T1 (70, 27)	<4.9 mo	−1.10	−0.48	−0.62 (−1.01, −0.22)	NS, $p_{[interaction]} = .94$
	T2 (71, 35)	4.9-8.6 mo	−1.07	−0.43	−0.65 (−1.00, −0.29)	
	T3 (62, 38)	≥8.7 mo	−0.92	−0.21	−0.71 (−1.06, −0.36)	
HOMA-IR	T1 (63, 34)	<2.8	−0.99	−0.32	−0.67 (−1.02, −0.32)	NS, $p_{[interaction]} = .37$
	T2 (59, 40)	2.8-5.5	−0.97	−0.50	−0.47 (−0.83, −0.12)	
	T3 (73, 22)	≥5.5	−1.10	−0.24	−0.86 (−1.28, −0.44)	

Note: A pattern mixture model was used to impute missing observations 1000 times based on patients who remained on therapy and were not given rescue medication within the liraglutide and placebo groups, respectively. For each of the imputed data sets, change in HbA1c from baseline to week 26 was analysed using an ANCOVA model with treatment, country, stratification by baseline metformin use and subgroup variable with interaction treatment and subgroup variable as categorical fixed effects, and baseline HbA1c as covariate. Estimated de jure treatment differences and CI were combined using Rubin's formula.

Abbreviations: ANCOVA, analysis of covariance; BMI, body mass index; CI, confidence interval; ETD, estimated treatment difference; HbA1c, glycated haemoglobin; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; NS, not significant; SGLT2i, sodium-glucose cotransporter-2 inhibitor; T1, low tertile; T2, middle tertile; T3, high tertile; T2D, type 2 diabetes.

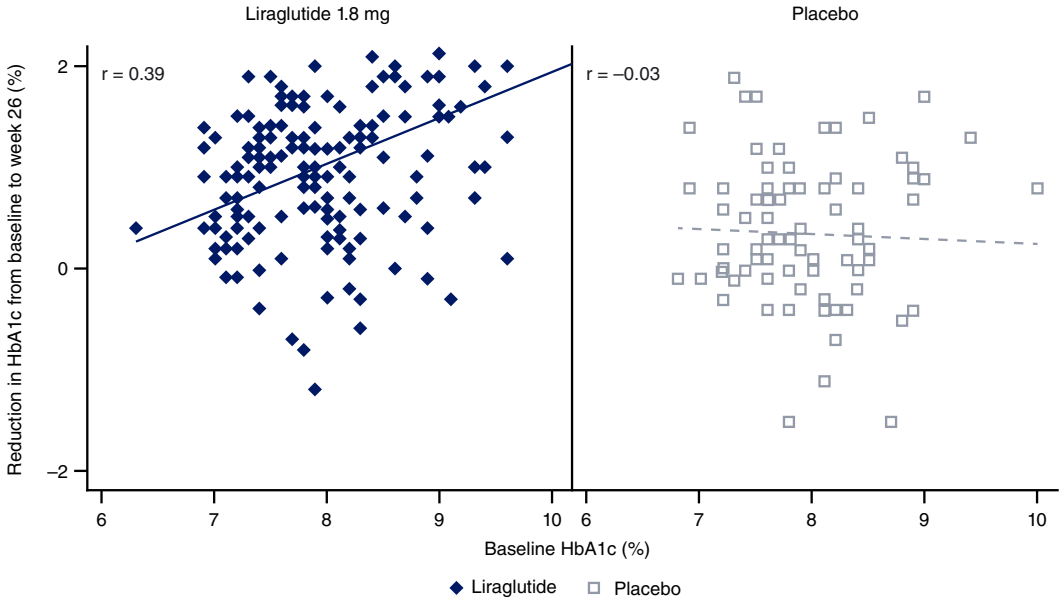

FIGURE 1 Scatterplot including correlations between overall changes in HbA1c from baseline to week 26 with the addition of liraglutide 1.8 mg versus placebo in patients with type 2 diabetes on stable sodium-glucose cotransporter-2 inhibitor therapy ± metformin (trial product estimand). A positive value on the vertical axis represents a reduction in HbA1c. Horizontal axis shows increasing baseline HbA1c values. HbA1c, glycated haemoglobin

TABLE 2 Treatment effect (trial product estimand) on change from baseline to week 26 in body weight by baseline characteristics when liraglutide 1.8 mg versus placebo was added to stable SGLT2i ± metformin therapy in patients with T2D

Baseline characteristic	Tertile [n (liraglutide 1.8 mg), n (placebo)]	Tertile cut-off values	Mean change in BW at week 26 (kg)		ETD (95% CI) at week 26 (kg)	*p*-value
			Liraglutide 1.8 mg	Placebo		
Overall change in BW[11]			−2.92	−2.06	−0.86 (−1.77, −0.04)	NS, $p = .06$
Baseline HbA1c	T1 (65, 27)	7.0%-<7.6%	−3.01	−3.21	0.20 (−1.52, 1.92)	NS, $p_{[interaction]} = .45$
	T2 (63, 35)	7.6%-8.1%	−2.86	−1.59	−1.26 (−2.86, 0.33)	
	T3 (75, 38)	≥8.2%-9.5%	−2.80	−1.85	−0.96 (−2.49, 0.57)	
BMI	T1 (75, 26)	<28.6 kg/m^2	−2.44	−1.30	−1.14 (−2.84, 0.57)	NS, $p_{[interaction]} = .89$
	T2 (61, 40)	28.6-33.9 kg/m^2	−2.74	−2.16	−0.58 (−2.09, 0.94)	
	T3 (67, 34)	≥34.0 kg/m^2	−3.52	−2.73	−0.80 (−2.43, 0.83)	
Diabetes duration	T1 (66, 35)	<5.6 y	−2.96	−1.83	−1.13 (−2.78, 0.50)	NS, $p_{[interaction]} = .85$
	T2 (69, 33)	5.6-11.6 y	−2.90	−2.35	−0.55 (−2.09, 0.99)	
	T3 (68, 32)	≥11.7 y	−2.81	−2.21	−0.60 (−2.21, 1.02)	
Duration of pre-trial SGLT2i use	T1 (70, 27)	<4.9 mo	−3.36	−2.00	−1.37 (−3.13, 0.39)	NS, $p_{[interaction]} = .67$
	T2 (71, 35)	4.9-8.6 mo	−2.68	−2.35	−0.33 (−1.89, 1.22)	
	T3 (62, 38)	≥8.7 mo	−2.59	−2.00	−0.59 (−2.14, 0.95)	
HOMA-IR	T1 (63, 34)	<2.8	−3.23	−2.01	−1.22 (−2.77, 0.33)	NS, $p_{[interaction]} = .63$
	T2 (59, 40)	2.8-5.5	−2.55	−2.36	−0.19 (−1.71, 1.33)	
	T3 (73, 22)	≥5.5	−2.68	−2.32	−0.36 (−2.22, 1.49)	

Note: A pattern mixture model was used to impute missing observations 1000 times based on patients who remained on therapy and were not given rescue medication within the liraglutide and placebo groups, respectively. For each of the imputed data sets, change in HbA1c from baseline to week 26 was analysed using an ANCOVA model with treatment, country, stratification by baseline metformin use and subgroup variable with interaction treatment and subgroup variable as categorical fixed effects, and baseline HbA1c as covariate. Estimated de jure treatment differences and CI were combined using Rubin's formula.

Abbreviations: ANCOVA, analysis of covariance; BMI, body mass index; BW, body weight; CI, confidence interval; ETD, estimated treatment difference; HbA1c, glycated haemoglobin; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; NS, not significant; SGLT2i, sodium-glucose cotransporter-2 inhibitor; T1, low tertile; T2, middle tertile; T3, high tertile; T2D, type 2 diabetes.

baseline HbA1c tertiles (Table 2). This could explain, at least in part, the greater mean reduction in HbA1c for those with a baseline HbA1c 7.0%-<7.6%, compared with other tertiles, observed in the placebo group.

Correlation analysis showed a trend for greater body weight reduction in patients with higher baseline BMI in both arms ($r = 0.14$ for liraglutide and $r = 0.26$ for placebo) (Figure 2). Similar findings were also observed for the treatment policy estimand (Table S3 and Figure S2, Appendix S1), including the results of exploratory analyses excluding data from the outlier (Table S4, Appendix S1).

3.4 | Changes in waist circumference by baseline characteristics

WC reductions were observed in both treatment groups at week 26 (ETD adjusted for baseline values: −2.01 cm; 95% CI: −4.04, 0.01, $p = .05$; trial product estimand; Table 3).[11] In both treatment groups, greater WC reductions were observed in patients in the baseline BMI <28.6 kg/m^2 tertile compared with the two higher baseline BMI tertiles (Table 3). However, there were no significant interactions among ETDs in WC between arms across any baseline characteristic assessed (Table 3). Similar findings were also observed for the treatment policy estimand (Table S5, Appendix S1).

4 | DISCUSSION

This post-hoc analysis evaluated whether the efficacy of liraglutide 1.8 mg, versus placebo, in addition to SGLT2i ± metformin on glycaemic control, body weight and WC was dependent on five baseline characteristics (HbA1c, BMI, duration of diabetes, duration of pre-trial SGLT2i use and HOMA-IR). The ETD for HbA1c was greater with higher HbA1c at baseline for liraglutide versus placebo, and no interaction was observed with the other four baseline characteristics. Regarding change in body weight and WC, no interaction was observed with all five baseline characteristics.

As expected with antihyperglycaemic drugs, the reductions in HbA1c with liraglutide versus placebo were larger for patients in the higher baseline HbA1c tertiles, compared with those in the lower

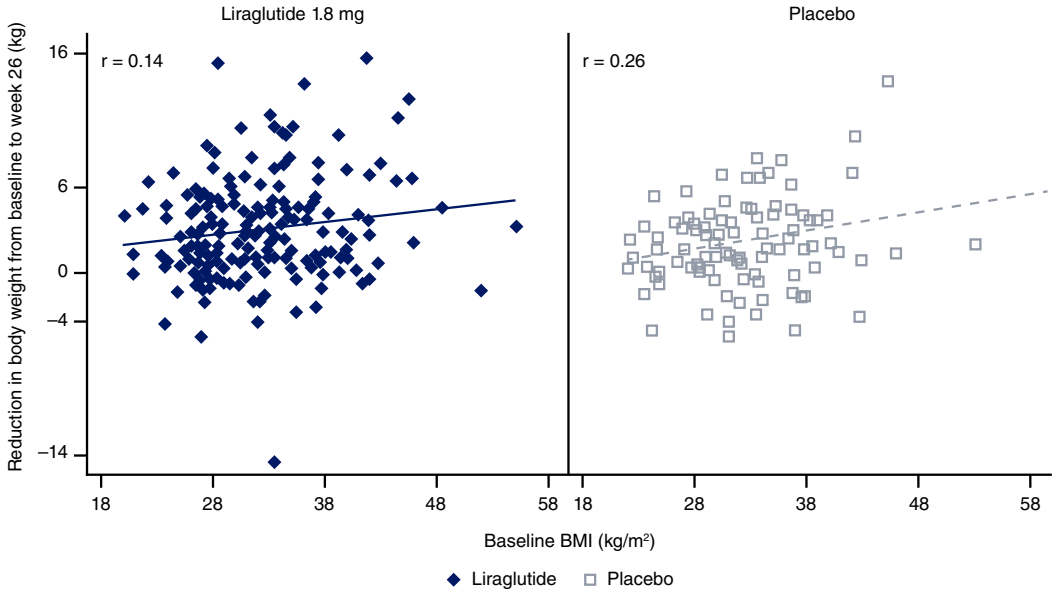

FIGURE 2 Scatterplots and correlation between overall changes in body weight from baseline to week 26 with the addition of liraglutide 1.8 mg versus placebo in patients with type 2 diabetes on stable sodium-glucose cotransporter-2 inhibitor therapy ± metformin (trial product estimand). A positive value on the vertical axis represents a reduction in body weight. Horizontal axis shows increasing baseline BMI values. BMI, body mass index

TABLE 3 Treatment effect (trial product estimand) on change from baseline to week 26 in waist circumference by baseline characteristics when liraglutide 1.8 mg versus placebo was added to stable SGLT2i ± metformin therapy in patients with T2D

Baseline characteristic	Tertile [n (liraglutide 1.8 mg), n (placebo)]	Tertile cut-off values	Mean change in WC at week 26 (cm)		ETD (95% CI) at week 26 (cm)	*p*-value
			Liraglutide 1.8 mg	Placebo		
Overall change in WC reported in LIRA-ADD2SGLT2i[1]			−4.26	−2.24	−2.01 (−4.04, 0.01)	NS, $p = .05$
Baseline HbA1c	T1 (65, 27)	7.0%-<7.6%	−4.19	−2.69	−1.51 (−5.45, 2.45)	NS, $p_{[interaction]} = .60$
	T2 (63, 35)	7.6%-8.1%	−4.44	−0.80	−3.64 (−7.33, 0.05)	
	T3 (75, 38)	≥8.2%-9.5%	−4.16	−3.03	−1.13 (−4.68, 2.42)	
BMI	T1 (75, 26)	<28.6 kg/m^2	−9.26	−8.03	−1.03 (−4.88, 2.43)	NS, $p_{[interaction]} = 1.00$
	T2 (61, 40)	28.6-33.9 kg/m^2	−4.35	−3.10	−1.25 (−4.50, 2.01)	
	T3 (67, 34)	≥34.0 kg/m^2	1.71	2.86	−1.15 (−4.65, 2.36)	
Diabetes duration	T1 (66, 35)	<5.6 y	−2.87	−1.10	−1.77 (−5.53, 1.99)	NS, $p_{[interaction]} = .96$
	T2 (69, 33)	5.6-11.6 y	−5.16	−2.67	−2.49 (−6.04, 1.05)	
	T3 (68, 32)	≥11.7 y	−4.70	−2.77	−1.92 (−5.62, 1.77)	
Duration of pre-trial SGLT2i use	T1 (70, 27)	<4.9 mo	−3.72	−3.58	−0.13 (−4.17, 3.91)	NS, $p_{[interaction]} = 0.21$
	T2 (71, 35)	4.9-8.6 mo	−4.26	−3.28	−0.98 (−4.62, 2.67)	
	T3 (62, 38)	≥8.7 mo	−4.82	−0.19	−4.64 (−8.17, −1.10)	
HOMA-IR	T1 (63, 34)	<2.8	−7.17	−4.76	−2.41 (−6.04, 1.22)	NS, $p_{[interaction]} = .75$
	T2 (59, 40)	2.8-5.5	−2.29	−1.14	−1.15 (−4.70, 2.39)	
	T3 (73, 22)	≥5.5	−3.28	−0.06	−3.22 (−7.52, 1.08)	

Note: A pattern mixture model was used to impute missing observations 1000 times based on patients who remained on therapy and were not given rescue medication within the liraglutide and placebo groups, respectively. For each of the imputed data sets, change in HOMA-IR from baseline to week 26 was analysed using an ANCOVA model with treatment, country, stratification by baseline metformin use and subgroup variable with interaction treatment and subgroup variable as categorical fixed effects, and baseline WC as covariate. Estimated de jure treatment differences and CI were combined using Rubin's formula.

Abbreviations: ANCOVA, analysis of covariance; BMI, body mass index; CI, confidence interval; ETD, estimated treatment difference; HbA1c, glycated haemoglobin; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; NS, not significant; SGLT2i, sodium-glucose cotransporter-2 inhibitor; T1, low tertile; T2, middle tertile; T3, high tertile; T2D, type 2 diabetes; WC, waist circumference.

tertiles. Unusually, while the ETDs for change in HbA1c from baseline to week 26 followed the pattern expected based on previously published literature,[18] these ETDs were driven by the placebo group, with the mean HbA1c change in the lowest tertile of the placebo group being quite high (at almost 0.9%), and the HbA1c reductions with liraglutide from baseline were not greater in those in the highest HbA1c tertile. These could be chance occurrences due to the small interval between the tertile cut-off values of 7.6% and 8.2%. Another potential reason is the low number of patients in the tertile subgroups, particularly those treated with placebo, exacerbated by the 2:1 randomization. It was also speculated that lifestyle interventions including diet and increased physical activity might have been particularly reinforced in patients in the lowest HbA1c tertile in an attempt to avoid the need for rescue therapy. Similar to the literature,[19,20] the largest body weight reduction was observed in the lowest HbA1c tertile, compared with the two higher HbA1c tertiles, for both liraglutide and placebo groups, which could further support this hypothesis. Furthermore, the difference in the correlation of HbA1c reduction between the liraglutide and placebo groups was much bigger ($r = 0.39$ and -0.03, respectively) compared with that for body weight reduction ($r = 0.14$ and 0.26, respectively). Importantly, reductions in HbA1c occurred regardless of changes in body weight or WC, as has previously been shown to occur with GLP-1 RA use.[8,10,21] This post-hoc analysis suggests that liraglutide added on to SGLT2i can provide beneficial glucose-lowering effects in a broad range of patients, independent of baseline BMI, diabetes duration and insulin resistance determined by HOMA-IR or duration of current SGLT2i use.

It is worth noting that the placebo data for body weight and WC were interesting. In both estimand analyses, the treatment effects on body weight and WC were noted to be in favour of placebo in the baseline HbA1c 7.0%-<7.6% tertile. The high placebo response for body weight and WC observed in the lowest tertile for baseline HbA1c in this trial has probably contributed to the HbA1c reduction with placebo in the lowest tertile. One explanation for the greater reduction in body weight and WC in the placebo group in this tertile may be due to the stipulation that all patients be on background SGLT2i therapy before trial commencement. As approximately half of these patients had only been on SGLT2i therapy for 3-6 months before randomization, it is possible that the body weight-lowering effect of SGLT2is was still ongoing during the treatment period and hence contributed to the weight and WC reduction in the placebo group. However, this one possible explanation may also apply to the other two tertiles.

Results from the DURATION 8 trial indicated that the combination of exenatide extended-release and an SGLT2i when initiated simultaneously (i.e. exenatide extended-release was not an add-on) had a synergistic 'effect on body weight'.[8] However, for AWARD 10, the effect on body weight of dulaglutide versus placebo (in which both were added on to SGLT2i) was relatively small, with only the highest dose of dulaglutide showing statistically significant body weight reductions compared with placebo.[9] Most recently, in SUSTAIN 9, the body weight reduction with once-weekly semaglutide versus placebo (both added to SGLT2i) was significant, probably due to the pronounced HbA1c- and weight-lowering effects of once-weekly semaglutide.[10] In the context of these previous trial results and when undertaking these post-hoc analyses of the LIRA-ADD2SGLT2i trial, we aimed to determine whether any differing baseline characteristics influenced the efficacy of liraglutide versus placebo in combination with SGLT2i. We found that the trial product estimand analyses on body weight reductions, performed excluding the outlier, aligned our findings to trends observed in trials with exenatide, dulaglutide and once-weekly semaglutide.[8-10]

In addition, in the initial analyses performed with the outlier, there were greater changes in body weight in patients with higher BMI. This result was in agreement with results in a previous liraglutide trial, which reported that higher baseline BMI was associated with increased reduction in body weight.[22] However, in our analysis, relative weight loss was somewhat higher in patients in lower BMI categories for both estimands without the outlier.

As this was a post-hoc subgroup analysis that was not pre-specified, there is the potential for selection bias. These results should also be interpreted with caution because the HbA1c tertiles (in particular) were narrow and sample sizes were small.

In conclusion, the results of this post-hoc analysis of the LIRA-ADD2SGLT2i trial suggest that in individuals with T2D and inadequate glycaemic control, despite treatment with an SGLT2i ± metformin, the addition of liraglutide 1.8 mg would provide an effective treatment intensification option irrespective of a broad range of baseline values for HbA1c, BMI, duration of diabetes, insulin resistance determined by HOMA-IR and duration of SGLT2i use. Furthermore, the benefit in HbA1c reduction appeared more pronounced in those with high baseline HbA1c. However, statistical significance for treatment differences in changes in body weight or WC was not achieved and cautious interpretation is needed, given the limitations presented. Nonetheless, the LIRA-ADD2SGLT2i trial and this post-hoc analysis provide further support for the combined use of an SGLT2i and a GLP-1 RA in the treatment of individuals with T2D. Indeed, this combination therapy is now an option that is recommended by a number of current national/international guidelines.[2,3]

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CONFLICT OF INTEREST

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PEER REVIEW

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DATA AVAILABILITY STATEMENT

The subject level analysis data sets for the research presented in the publication are available from the corresponding author on reasonable request.

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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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