Liraglutide as add-on to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes: a 26-week, randomised, double-blind, placebo-controlled trial

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Background

- Type 2 diabetes (T2D) is a progressive disease typically requiring treatment intensification to achieve and/or maintain good glycaemic control;[1] this can be achieved through combining therapies that have complementary mechanisms of action.
- Both glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter-2 inhibitors (SGLT2is) are associated with improved glycaemic control, low rates of hypoglycaemia, reductions in body weight, cardiovascular benefits and a favourable safety profile in patients with T2D.[1–3]
- Despite limited evidence for the concomitant use of GLP-1 receptor agonists with SGLT2is,[4–5] the combination of these drug classes has been increasingly used by clinicians, and is now recommended by guidelines.[1]
- The LIRA-ADD2SGLT2i trial assessed the effect on glycaemic control of the GLP-1 analogue liraglutide, versus placebo, when administered in combination with an SGLT2i (± metformin) in patients with inadequate glycaemic control.
- This trial addresses limitations in the available data for combined use of these drugs, aiming to strengthen the scientific rationale behind clinical decisions for the management of T2D.

Methods

Study design

- LIRA-ADD2SGLT2i (NCT02964247) was a 26-week, double-blind, randomised, placebo-controlled, parallel-arm, multicentre, multinational phase 3b trial.
- Enrolled patients had T2D, glycated haemoglobin (HbA_{1c}) levels of 7.0–9.5%, body mass index (BMI) ≥20 kg/m^2, received a stable dose of SGLT2i (canagliflozin, dapagliflozin or empagliflozin) for at least 90 days as monotherapy or in combination with a stable dose of metformin (≥1500 mg or maximum tolerated dose), no history of diabetic ketoacidosis (DKA) while on SGLT2i, and had an estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2.
- Patients were randomised 2:1 to receive either liraglutide 1.8 mg or placebo, added to a continuous stable treatment with an SGLT2i ± metformin for 26 weeks with a subsequent 1-week follow-up.
- The primary endpoint was change in HbA_{1c} from baseline to 26 weeks.
- Secondary assessments included: change in body weight from baseline, proportion of patients achieving HbA_{1c} <7% and ≤6.5% and safety.

Statistical analysis

- Two distinct statistical approaches were used to address different aspects of the treatment effect.
- The treatment policy estimand (primary estimand) was analysed with a pattern mixture model; it evaluated the average treatment effect of adding liraglutide versus placebo to a stable regimen of SGLT2i with or without metformin in all randomised patients, regardless of adherence to treatment or use of rescue glucose-lowering medication (i.e. effectiveness).
- The trial product estimand (secondary estimand) was estimated using a mixed model for repeated measurements; it evaluated the average treatment effect of adding liraglutide to stable SGLT2i with or without metformin treatment for all randomised patients, under the assumption that all patients remained on trial product for the entire planned duration of the trial and did not use rescue glucose-lowering treatment (i.e. efficacy).

Results

- Of the 412 patients screened, 303 were randomised to either liraglutide (203) or placebo (100); 280 patients (92.4%) completed treatment (92.1% vs 93.0% for liraglutide and placebo, respectively).
- Baseline characteristics were balanced across both arms (Table 1).
- At week 26, the mean change in HbA_{1c} from baseline was –0.98% for the liraglutide group vs –0.30% for the placebo group, with an estimated treatment difference (ETD) of –0.68% (95% confidence interval [CI] –0.89, –0.48; p<0.001 [Figure 1]).
- The mean change in body weight was –2.81 kg vs –1.99 kg for the liraglutide and placebo groups, respectively (ETD –0.82 kg; 95% CI –1.73, 0.09; p=0.077 [Figure 2]).
- A higher proportion of patients in the liraglutide group versus placebo (Figure 3) achieved:
  - HbA_{1c} <7.0%;
  - HbA_{1c} ≤6.5%.

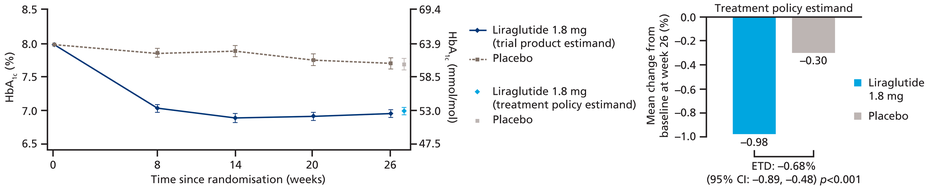
Table 1: Baseline demographics and clinical characteristics

Mean (SD)	Liraglutide 1.8 mg N=203	Placebo N=100	Total N=303
Sex (% males)	62	58	60
Age, years	54.7 (10.1)	56.0 (9.9)	55.2 (10.0)
Diabetes duration, years	10.1 (7.2)	9.6 (6.7)	9.9 (7.0)
HbA_{1c}, mmol/mol	63.9 (8.0)	63.4 (6.9)	63.8 (7.6)
HbA_{1c}, %	8.0 (0.7)	8.0 (0.6)	8.0 (0.7)
FPG, mg/dL	160.7 (41.7)	159.1 (46.3)	160.2 (43.2)
FPG, mmol/L	8.9 (2.3)	8.8 (2.6)	8.9 (2.4)
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)
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 and metformin use, N (%)			
SGLT2i			
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)

BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin; SBP, systolic blood pressure; SD, standard deviation; SGLT2i, sodium-glucose cotransporter-2 inhibitor

Figure 1: Change in HbA_{1c} from baseline

Key result



Estimated treatment effect was calculated using treatment policy estimands with a 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 MMRM were based on the on-treatment without rescue medication observation period. CI, confidence interval; ETD, estimated treatment difference; HbA_{1c}, glycated haemoglobin; MMRM, mixed model of repeated measurements; PMM, pattern mixture model

Figure 2: Change in body weight from baseline

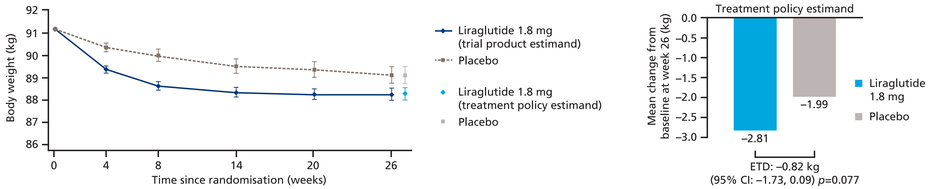


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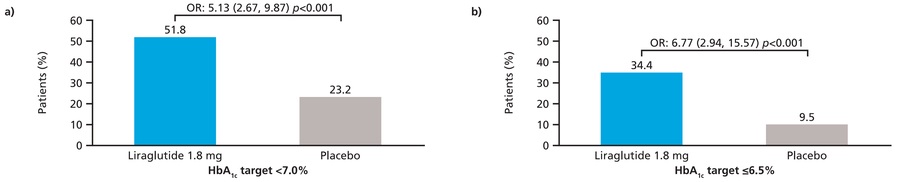
Figure 3: Proportion of patients reaching HbA_{1c} targets (at week 26): a) HbA_{1c} target <7.0%, b) HbA_{1c} target ≤6.5%



HbA_{1c}, glycated haemoglobin; OR, odds ratio

- A higher proportion of patients reported ≥1 treatment-emergent adverse event (AE) in the liraglutide group than the placebo group (66.3 vs 47.0%, respectively [Table 2]).
  - Nausea was the most commonly reported AE (26.2% and 6.0% for liraglutide versus placebo, respectively) and was predominately early-onset and transient.
  - Serious AEs were reported by a low proportion of patients in both liraglutide (2.5%) and placebo (1.0%) groups and there were no fatalities, reports of acute renal failure, DKA, diabetic foot ulcers or amputations with liraglutide in combination with an SGLT2i.
  - The proportion of patients reporting hypoglycaemia was similar across liraglutide (8.9%) and placebo (8.0%) groups, and none of these episodes were severe (defined as requiring assistance from another person according to the American Diabetes Association criterion).[6]

Table 2: Summary of adverse events

	Liraglutide 1.8 mg N=202 n (%)	Placebo N=100 n (%)
Deaths	0 (0.0)	0 (0.0)
Serious adverse events*	5 (2.5)	1 (1.0)
Treatment-emergent adverse events[†]	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 due to adverse events	8 (4.0)	2 (2.0)
All hypoglycaemic episodes	18 (8.9)	8 (8.0)
Severe or BG-confirmed symptomatic[†]	0 (0.0)	3 (3.0)[#]
Severe (ADA)	0 (0.0)	0 (0.0)

Data presented are from the safety analysis set. *One serious adverse event (cholecystitis in the liraglutide group) was judged by the investigator as possibly or probably related to trial product, which led to premature trial product discontinuation for the remainder of the trial. The event had resolved by the end of the trial. No cases of acute pancreatitis or medullary thyroid cancer were reported. Hypoglycaemia plasma glucose cut-off: [†]Novo Nordisk definition is <3.1 mmol/L (56 mg/dL); ADA level 1 definition is 3.0–3.9 mmol/L (≥54–<70 mg/dL). [#]One patient was on rescue medication with sulphonylureas. %, proportion of patients; ADA, American Diabetes Association; BG, blood glucose; N, number of patient.

Conclusions

- In patients with T2D, the addition of liraglutide to SGLT2i therapy (± metformin) provided superior glycaemic control versus placebo, with safety profiles consistent with that of both drug classes.
- The LIRA-ADD2SGLT2i trial provides clinical evidence to support use of GLP-1 analogues with SGLT2is to help improve glycaemic control.

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References: (**1**) Davies, *et al. Diabetes Care* 2018;41:2669–701; (**2**) Marso *et al. N Engl J Med* 2016;375:311–22; (**3**) Zinman *et al. N Engl J Med* 2015;373:2117–28; (**4**) Ludvik *et al. Lancet Diabetes Endocrinol* 2018;6:370–81; (**5**) Frías *et al. Lancet Diabetes Endocrinol* 2016;4:1004–16; (**6**) American Diabetes Association. *Diabetes Care* 2005;28:1245–49.