

ORIGINAL ARTICLE

Efficacy and safety of switching from sitagliptin to liraglutide in subjects with type 2 diabetes (LIRA-SWITCH): a randomized, double-blind, double-dummy, active-controlled 26-week trial

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Aims: To confirm superiority on glycaemic control by switching from sitagliptin to liraglutide 1.8 mg/d versus continued sitagliptin.

Materials and methods: A randomized, multicentre, double-blind, double-dummy, active-controlled trial across 86 office- or hospital-based sites in North America, Europe and Asia. Subjects with type 2 diabetes who had inadequate glycaemic control (glycated haemoglobin [HbA1c] 7.5–9.5% on sitagliptin (100 mg/d) and metformin (≥ 1500 mg daily) for ≥ 90 days were randomized to either switch to liraglutide ($n = 203$) or continue sitagliptin ($n = 204$), both with metformin. The primary endpoint was change in HbA1c from baseline to week 26. Change in body weight was a confirmatory secondary endpoint.

Results: Greater reduction in mean HbA1c was achieved with liraglutide than with continued sitagliptin [−1.14% vs. −0.54%; estimated mean treatment difference (ETD): −0.61% (95% CI −0.82 to −0.40; $p < 0.0001$)], confirming superiority of switching to liraglutide. Body weight was reduced more with liraglutide [−3.31 kg vs. −1.64 kg; ETD: −1.67 kg (95% CI −2.34 to −0.99; $p < 0.0001$)]. Nausea was more common with liraglutide [44 subjects (21.8%)] than with continued sitagliptin [16 (7.8%)]. Three subjects (1.5%) taking sitagliptin reported a confirmed hypoglycaemic episode.

Conclusions: Subjects insufficiently controlled with sitagliptin who switch to liraglutide can obtain clinically relevant reductions in glycaemia and body weight, without compromising safety. A switch from sitagliptin to liraglutide provides an option for improved management of type 2 diabetes while still allowing patients to remain on dual therapy.

KEYWORDS

liraglutide, sitagliptin, type 2 diabetes, GLP-1 receptor agonist

1 | INTRODUCTION

Hyperglycaemia management in type 2 diabetes (T2D) requires a patient-centred approach, with therapy choice dependent on various patient- and disease-specific factors.^{1,2} When diet and exercise are insufficient, patients are generally started on metformin, and when intensification is required, a second oral antidiabetic drug (OAD), injectable glucagon-like peptide-1 receptor agonists (GLP-1RAs) or insulin, is equally recommended as second-line therapy by the

American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) position statement.²

Liraglutide is a GLP-1RA for treatment of T2D that offers effective glycaemic control, benefits in weight reduction, improved measures of β -cell function (homeostatic model assessment of β -cell function [HOMA-B]) and a lower risk of hypoglycaemia than with insulin and selected OADs.^{3,4} Sitagliptin is a dipeptidyl peptidase-4 inhibitor (DPP-4i), also shown to improve glycaemic control and HOMA-B in patients with T2D.^{5,6} DPP-4is and GLP-1RAs represent

two different therapy classes; GLP-1RAs promote GLP-1 receptor signalling via stimulation through circulating "incretin mimetics"; DPP-4is prevent degradation of endogenously released GLP-1 in connection with meals.⁷ Whereas DPP-4is may be associated with fewer gastrointestinal (GI) adverse events (AEs) than GLP-1RAs, clinical trials have shown that GLP-1RAs are superior to DPP-4is regarding glycaemic control and body weight reduction when tested head-to-head.^{8,9} However, limited clinical evidence exists to guide treatment strategy when initial second-line treatment with sitagliptin fails to provide adequate glycaemic control.

A previous head-to-head, open-label, phase 4 clinical trial demonstrated that liraglutide 1.2 mg and 1.8 mg were superior to sitagliptin after 52 weeks regarding glycated haemoglobin (HbA1c) reduction, proportion of subjects reaching the ADA HbA1c target and body weight reduction.¹⁰ Furthermore, an extension of that trial demonstrated that switching subjects from sitagliptin to liraglutide 1.2 mg and 1.8 mg, respectively, after 52 weeks of treatment resulted in additional and statistically significant reduction in HbA1c at week 78. These latter extension data were obtained, however, without a formal control group.¹¹

Based on these previous open-label, uncontrolled data, it was hypothesized that by switching insufficiently controlled subjects from metformin + sitagliptin to metformin + liraglutide, more patients with T2D would achieve better glycaemic control in terms of HbA1c reduction, with an associated reduction in body weight while still being on dual therapy. Accordingly, the primary objective of this trial was to confirm superiority on glycaemic control by switching from sitagliptin 100 mg/d to liraglutide 1.8 mg/d versus continued sitagliptin 100 mg/d, in subjects on unchanged metformin therapy. Secondary objectives were to compare effects of switching from sitagliptin to liraglutide (vs. continued sitagliptin) on body weight, selected cardiovascular risk factors, safety and tolerability. Results of this trial would be expected to further inform clinical decision-making for patients with T2D.

2 | RESEARCH DESIGN AND METHODS

2.1 | Participants

Inclusion criteria were: T2D, age ≥ 18 years, HbA1c 7.5–9.5%, body mass index (BMI) ≥ 20 kg/m², previous treatment with stable doses of sitagliptin (100 mg/d) and metformin [≥ 1500 mg/d or maximum tolerated dose (MTD) ≥ 1000 mg/d] for ≥ 90 days. See Appendix S1 for exclusion criteria.

The study was conducted in accordance with the Declaration of Helsinki,¹² good clinical practice guidelines¹³ and was approved by independent ethics committees. Informed consent was obtained before any trial-related activity.

2.2 | Study design

This trial (LIRA-SWITCH) was a phase 4, 26-week, randomized, multicentre, parallel-group, double-blind, double-dummy, active-controlled trial conducted across 86 office- or hospital-based sites

in the USA, Canada, Hungary, Israel, India and Spain between December 2013 and June 2015. A total of 407 subjects were randomized 1:1 to one of two study arms (using interactive voice/web response system [IV/WRS]): liraglutide (subcutaneously) at a starting dose of 0.6 mg/d, with weekly dose escalations of 0.6 mg/d until the maintenance dose of 1.8 mg/d was reached, plus once-daily sitagliptin placebo tablets versus oral sitagliptin tablets (100 mg/d) plus liraglutide placebo (subcutaneously) mirroring dose escalation of the active liraglutide arm. Both arms continued metformin at pre-trial dose. Subjects were stratified according to baseline HbA1c ($\leq 8.5\%$ and $> 8.5\%$) and metformin dose (< 1500 and ≥ 1500 mg/d). After randomization, a 26-week treatment period was completed, followed by a 1-week follow-up period.

For subjects meeting predefined hyperglycaemia criteria, predefined criteria for discontinuation of trial products or withdrawal from the trial, protocol amendments, and method of assigning subjects to treatments, please see Appendices S2–S5.

2.3 | Study measurements

2.3.1 | Efficacy

The primary endpoint was change in HbA1c from baseline to week 26. A confirmatory secondary endpoint was change in body weight from baseline to week 26. Other secondary endpoints included: change in fasting plasma glucose (FPG); change in systolic (SBP) and diastolic blood pressure (DBP) and change in fasting blood lipid levels; subjects meeting HbA1c targets $< 7.0\%$ (ADA target) and $\leq 6.5\%$ (American Association of Clinical Endocrinologists target); composite endpoints including subjects achieving HbA1c reduction of $\geq 1.0\%$ and no weight gain; HbA1c $< 7.0\%$ and no weight gain; HbA1c $< 7.0\%$, no weight gain and SBP < 140 mm Hg.

2.3.2 | Safety

Safety endpoints included the number of treatment-emergent adverse events (TEAEs), hypoglycaemic episodes during trial treatment (confirmed and ADA-classified episodes; see Table 1 for definitions), changes in haematological and biochemical laboratory parameters (including lipase and amylase) and change in pulse.

2.4 | Statistical analysis

The sample size, based on the test of the treatment difference in change from baseline in HbA1c after 26 weeks, was determined to be able to detect, with a 90% probability, a mean difference of 0.4% for liraglutide vs. sitagliptin, at a 5% significance level. Efficacy endpoints were assessed using the full analysis set (FAS), including all randomized subjects receiving at least one dose of any of the trial products. The statistical evaluation of the FAS followed the intention-to-treat (ITT) principle. Safety endpoints were assessed using the safety analysis set (SAS), including all subjects receiving at least one dose of any of the trial products. Subjects in the safety set contributed to the evaluation "as treated". Data collected after subjects initiated rescue treatment or discontinued trial medication were considered as missing in all analyses.

TABLE 1 Summary of treatment-emergent adverse events and hypoglycaemic episodes with liraglutide or sitagliptin

	Liraglutide		Sitagliptin	
	N (%)	E	N (%)	E
Number of subjects	202 (100)		204 (100)	
Total AEs	139 (68.8)	455	116 (56.9)	318
Serious AEs	6 (3.0)	8	7 (3.4)	8
Most common AEs (≥5% by preferred term)				
Nausea	44 (21.8)	59	16 (7.8)	21
Diarrhoea	33 (16.3)	45	19 (9.3)	21
Decreased appetite	18 (8.9)	18	7 (3.4)	7
Vomiting	15 (7.4)	18	10 (4.9)	15
Headache	13 (6.4)	16	12 (5.9)	16
Nasopharyngitis	12 (5.9)	14	7 (3.4)	7
Lipase increased	11 (5.5)	12	9 (4.4)	9
Amylase increased	4 (2.0)	4	4 (2.0)	4
Hypoglycaemic episodes				
Confirmed	0		3 (1.5)	3
ADA classification				
Severe	0		0	
Documented symptomatic	3 (1.5)	4	3 (1.5)	6
Asymptomatic	5 (2.5)	5	5 (2.5)	13
Probable symptomatic	1 (0.5)	2	1 (0.5)	1
Relative	3 (1.5)	3	0	
Unclassified	0	0	0	0

Confirmed hypoglycaemic episode: patients unable to treat themselves (severe hypoglycaemic episode) and/or with a plasma glucose reading <3.1 mmol/L (56 mg/dL).

%, percentage of subjects experiencing at least one event; ADA, American Diabetes Association; AE, adverse event; E, number of events (except for where number of hypoglycaemic episodes); N, number of subjects experiencing at least one event.

The primary endpoint, confirmatory secondary endpoint and other continuous secondary endpoints were analysed with the mixed model for repeated measurements (MMRM). If superiority was confirmed for the primary endpoint, the confirmatory secondary endpoint (change in body weight) was to be tested for superiority of liraglutide over sitagliptin. For the primary and secondary confirmatory endpoints, the MMRM included treatment, baseline HbA_{1c} level, metformin dose, the interaction between baseline HbA_{1c} level and metformin dose and country as factors, and the value of the response variable at baseline as a covariate, all variables nested within week as a factor. An unstructured covariance matrix was used to describe the variability for the repeated measurements for a subject.

Dichotomous endpoints were analysed by a logistic regression model. Effects in the model were treatment, baseline HbA_{1c} level (<8.5% and >8.5%), metformin dose (<1500 and ≥1500 mg/d), the interaction between baseline HbA_{1c} level and metformin dose and country as factors, and baseline HbA_{1c} as a covariate.

All safety endpoints were summarized descriptively using the SAS. Continuous safety endpoints were analysed by a method similar to that of the primary analysis. The significance level was set at 5% (two-sided tests).

3 | RESULTS

3.1 | Baseline characteristics and subject disposition

Study arms were well matched for demographic and other characteristics at baseline (Table 2).

Of the 814 subjects screened, 407 were randomized and 406 were exposed to trial medication. The trial was completed without treatment discontinuation or rescue medication by 159 (78.3%) subjects taking liraglutide and 157 (77%) taking sitagliptin. Rescue medication was required, respectively, by 11 (5.4%, liraglutide) and 30 subjects (14.7%, sitagliptin). More subjects prematurely discontinued liraglutide (21 subjects, 10.3%) than sitagliptin (8 subjects, 3.9%) (Figure 1). GI AEs leading to treatment discontinuation were only in the liraglutide group (9 subjects, 4.5%). To avoid missing data, subjects were encouraged to remain in the trial and complete end-of-trial and follow-up visits even after permanently discontinuing trial product.

3.2 | Primary efficacy assessments

3.2.1 | Change in HbA_{1c}

Switching from sitagliptin to liraglutide led to greater reduction in HbA_{1c} versus continuing sitagliptin (ETD -0.61%, -1.14% vs. -0.54%; 95% CI -0.82 to -0.40; $p < 0.0001$), thus confirming the superiority of liraglutide (Figure 2A).

3.3 | Confirmatory secondary endpoint

3.3.1 | Change in body weight

Significantly greater weight loss with liraglutide was observed compared with sitagliptin (ETD -1.67 kg, -3.31 kg vs. -1.64 kg; 95% CI -2.34 to -0.99; $p < 0.0001$) (Figure 2B). Superiority of liraglutide over sitagliptin on body weight reduction was confirmed by hierarchical testing after the primary endpoint.

3.4 | Secondary efficacy assessments

3.4.1 | Fasting plasma glucose

FPG decreased significantly more with liraglutide than with sitagliptin (ETD -1.10 mmol/L, -1.84 mmol/L vs. -0.73 mmol/L; 95% CI -1.50 to -0.71; $p < 0.0001$) (Figure 2C).

3.4.2 | Change in blood pressure

SBP change was not significantly different with liraglutide versus sitagliptin after 26 weeks of treatment: -4.05 versus -2.18 mm Hg; ETD -1.87 (95% CI -4.28 to 0.53, $p = 0.1264$). Change in DBP was not significantly different comparing liraglutide with sitagliptin: -0.27 versus -0.68 mm Hg; ETD 0.41 (95% CI -1.02 to 1.85, $p = 0.5730$).

3.4.3 | Fasting blood lipids

Minor changes in lipid parameters were observed for both liraglutide and sitagliptin. There was no difference in fasting blood lipids at week 26 between the two treatments (Figure S1).

TABLE 2 Baseline characteristics of subjects randomized to either liraglutide or sitagliptin

	Liraglutide	Sitagliptin
Safety analysis set, N	202	204
Age, years	56.3 (10.6)	56.5 (9.7)
Range	28.0-86.0	26.0-83.0
Duration of diabetes, years	7.9 (5.7)	7.6 (6.2)
Range	0.3-33.3	0.3-34.3
Female; Male (%)	42%; 58%	39%; 61%
Weight, kg	88.9 (19.8)	91.2 (19.6)
Range	53.0-173.9	46.5-167.8
Height, m	1.67 (0.10)	1.68 (0.10)
Range	1.43-1.95	1.42-1.91
BMI, kg/m ²	31.7 (6.0)	32.2 (6.2)
Range	20.0-55.0	20.2-58.1
Waist circumference, cm	106.9 (14.8)	106.9 (14.4)
Range	66.0-168.7	68.6-153.5
FPG, mmol/L [mg/dL]	10.0 (181) [2.7 (48.1)]	9.7 (174.1) [2.5(44.5)]
Range	3.8-21.8 (68.5-392.8)	4.5-19.2 (81.1-346.0)
HbA1c, % [mmol/mol]	8.3 (67) [0.6 (7)]	8.2 (67) [0.6 (7)]
Range	(6.3-10.7)	(5.7-10.1)
Systolic blood pressure, mm Hg	130.5 (14.4)	132.1 (12.1)
Range	99.0-178.0	96.0-171.0
Diastolic blood pressure, mm Hg	79.0 (8.1)	78.9 (7.6)
Range	49.0-98.0	50.0-96.0

Mean (SD) if not otherwise stated. BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; SD, standard deviation.

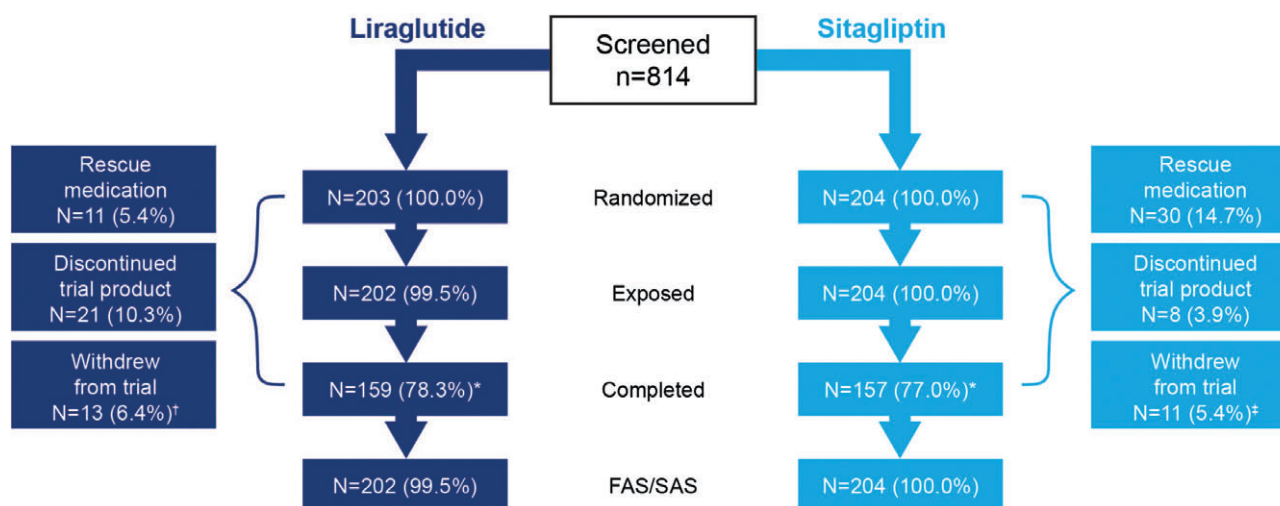


FIGURE 1 Flow of subjects through the study. *Without treatment discontinuation or rescue medication. †Two subjects in the liraglutide group and one in the sitagliptin group had the trial product discontinued and were thereafter withdrawn. ‡One subject in the sitagliptin group received rescue treatment and was thereafter withdrawn. FAS and SAS include all randomized subjects receiving at least one dose of any of the trial products. FAS, full analysis set; SAS, safety analysis set.

3.4.4 | Percentage of subjects reaching HbA1c <7.0% and ≤6.5%

After 26 weeks, a significantly higher proportion of subjects achieved HbA1c targets of <7.0% and ≤6.5% with liraglutide than with sitagliptin. Proportions of subjects achieving the target of <7.0% were: 50.6% versus 26.9% with liraglutide and sitagliptin, respectively, odds ratio (OR): 3.36 (95% CI 2.08-5.42, $p < 0.0001$). Proportions achieving the target of ≤6.5% were: 29.5% versus 9.9% with liraglutide and sitagliptin, respectively, OR: 5.44 (95% CI 2.82-10.47, $p < 0.0001$) (Figure 3).

3.4.5 | Percentage of subjects achieving composite endpoints

After 26 weeks, a significantly higher proportion of subjects achieved the composite endpoints with liraglutide than with sitagliptin. Proportions of subjects achieving the composite endpoint of HbA1c reduction ≥1.0% and no weight gain were: 52.8% versus 29.1% (liraglutide vs. sitagliptin), OR: 2.85 (95% CI 1.82-4.47, $p < 0.0001$). Proportions of subjects achieving the composite endpoint of HbA1c <7.0% and no weight gain were: 48.3% versus 24.2% (liraglutide vs. sitagliptin),

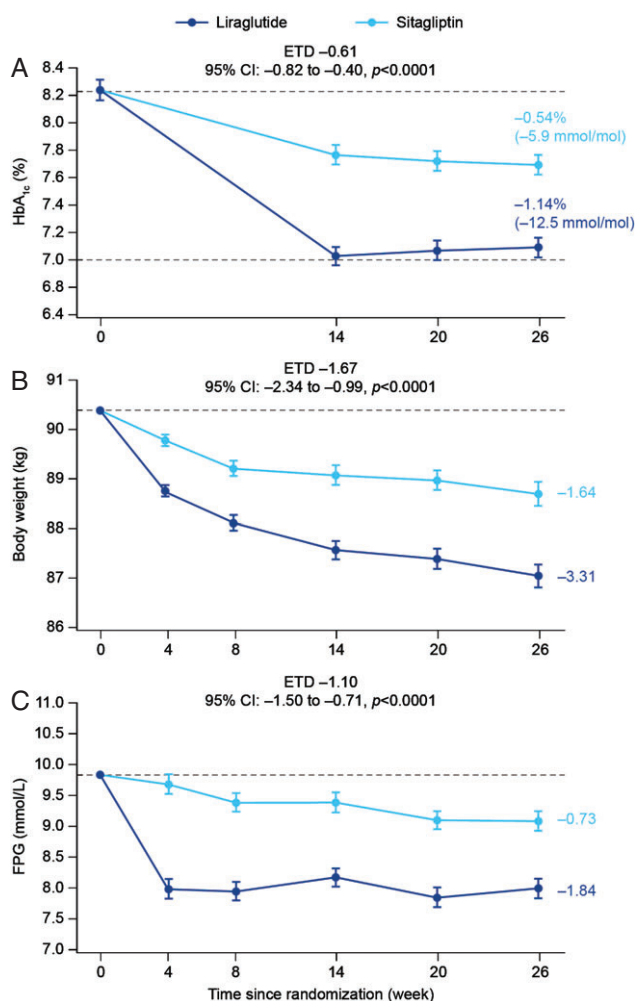


FIGURE 2 Mean change in HbA_{1c} (A), body weight (B) and FPG (C) from baseline after 26 weeks of treatment. On-treatment summary without rescue data. Group mean estimates (\pm SEM) are from a mixed model for repeat measurements (MMRM) with treatment, strata, country and baseline value, all nested within visit, and are adjusted according to observed baseline distribution. ETD, estimated treatment difference; FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin; SEM, standard error of the mean.

OR: 3.40 (95% CI 2.11–5.49, $p < 0.0001$). Proportions of subjects achieving the composite endpoint of HbA_{1c} $< 7.0\%$, no weight gain and SBP < 140 mm Hg were: 44.9% versus 19.2% (liraglutide vs. sitagliptin), OR: 3.88 (95% CI 2.36–6.39, $p < 0.0001$) (Figure S2).

3.5 | Safety endpoints

As expected, subjects who discontinued sitagliptin and switched to liraglutide experienced more AEs than those continuing on sitagliptin (68.8% vs. 56.9%; Table 1). Incidence of serious AEs was low in both groups: eight events per group [six subjects taking liraglutide (3.0%) and seven subjects taking sitagliptin (3.4%)]. There was one non-treatment-emergent death in the liraglutide group, judged 'unlikely related' to liraglutide by the investigator.

The most common TEAEs considered possibly/probably related to liraglutide were GI (nausea and diarrhoea) and metabolism and nutrition disorders (decreased appetite), particularly during the first 4 weeks of treatment. The proportion of subjects with GI AEs was

higher with liraglutide (40.1%) than sitagliptin (20.6%). Nausea (21.8% vs. 7.8%, Figure S3), vomiting (7.4% vs. 4.9%), diarrhoea (16.3% vs. 9.3%) and decreased appetite (8.9% vs. 3.4%) were all more frequent with liraglutide than with sitagliptin (see Figure S4 for incidence of All GI AEs). There was no incidence of pancreatitis or malignant neoplasms reported with liraglutide during the trial, but there were two malignant neoplasms in the sitagliptin group (bladder cancer and squamous cell carcinoma of skin, both assessed by the investigator as 'unlikely unrelated' to trial product). The proportion of subjects with AEs leading to premature treatment discontinuation was higher with liraglutide than with sitagliptin, mainly driven by GI AEs (treatment discontinuation due to AEs: 6.4% (4.5% GI AEs) for liraglutide and 2.5% (0% GI AEs) for sitagliptin).

No severe hypoglycaemic episodes were reported. Confirmed hypoglycaemic episodes were rare: three episodes for three subjects with sitagliptin (1.5%), of whom two subjects were on rescue therapy with insulin and sulphonylurea, respectively.

Pulse rate increased by 2.57 beats per minute (bpm) for liraglutide and decreased by -0.10 bpm for sitagliptin: ETD 2.67 bpm (95% CI 1.07–4.27; $p = 0.0011$).

Increases were observed in serum amylase for both liraglutide (8%) and sitagliptin (4%); the difference between treatment groups was not statistically significant: estimated treatment ratio (ETR): 1.03 (95% CI 0.98–1.09; $p = 0.2363$). A greater increase was observed in serum lipase for liraglutide (11%) versus sitagliptin (1%), a statistically significant difference [ETR 1.10 (95% CI 1.00–1.21; $p = 0.0392$)].

4 | CONCLUSIONS

The present study showed that, in subjects with T2D with elevated HbA_{1c} on dual combination treatment with sitagliptin + metformin, switching from sitagliptin to liraglutide was associated with improved glycaemic control and weight reduction compared with continued sitagliptin. During the trial, subjects who remained on sitagliptin tended to improve in these outcomes, but switching to liraglutide was significantly more efficacious. Improved blood glucose control with liraglutide was achieved with acceptable tolerability; hypoglycaemia was very rare, and other clinical endpoints such as blood pressure and lipids showed favourable or clinically insignificant changes.

These results also emphasize the importance of generally differentiating between the DPP-4i and GLP-1RA classes, since further improvement in glycaemic control can be achieved by substituting sitagliptin for liraglutide, as was originally suggested by the LIRA-DPP-4 main and extension trials.^{8,10}

When comparing baseline characteristics and findings of the LIRA-DPP-4 trial with the present trial (there was a lower HbA_{1c} at baseline in the LIRA-DPP-4 trial of 7.6%) when all subjects, regardless of their HbA_{1c}, were switched from sitagliptin to liraglutide, HbA_{1c} was then further reduced by -0.45% with liraglutide 1.8 mg after 26 weeks. In the present trial, baseline HbA_{1c} was higher (8.3%) and change from baseline with liraglutide 1.8 mg was -1.14% , with a corresponding ETD between liraglutide 1.8 mg and sitagliptin of -0.61% . The difference in change from baseline is probably related to differences in HbA_{1c} at time of switching.

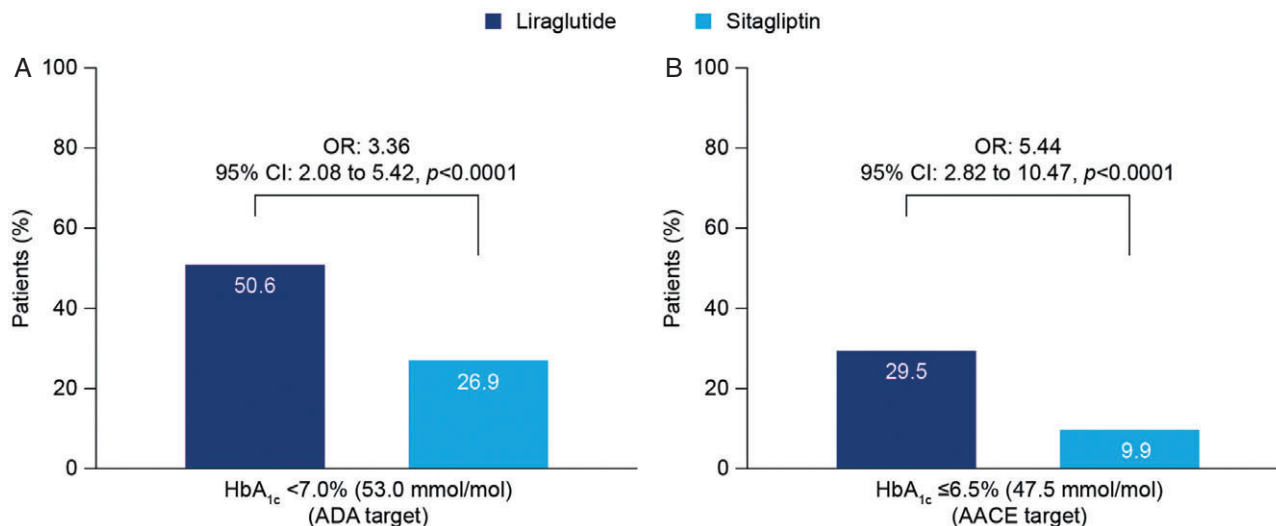


FIGURE 3 Subjects meeting HbA_{1c} targets for (A) ADA and (B) AACE after 26 weeks of treatment. On-treatment without rescue data with mixed model for repeated measurement (MMRM) imputation: subjects meeting targets (%) and estimated odds ratio based on logistic regression model with treatment, strata, metformin dose and country as fixed factors and the HbA_{1c} value at baseline as a covariate. AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association; HbA_{1c}, glycated haemoglobin; OR, odds ratio.

As subjects in the sitagliptin arm were continuing current therapy, the fairly similar overall proportions of subjects reporting AEs and severe AEs with liraglutide and sitagliptin were reassuring. AEs in the liraglutide group were mainly driven by GI AEs, which also were the main reason for a higher rate of subjects discontinuing the trial drug because of AEs.

It is important to consider that subjects in the sitagliptin + metformin arm were continuing on therapy that they were accustomed to. Also, subjects who switched from sitagliptin to liraglutide had already been used to some level of therapy that mediates its effect via the incretin pathway (albeit different treatment classes); therefore, the level of GI side effects might not be representative for a patient commencing liraglutide without previously having experienced sitagliptin treatment. However, in the original LIRA-DPP-4 study, rates of GI AEs were similar to those in this trial.⁸

It is known that up to 25% of subjects with T2D have elevated amylase or lipase levels,¹⁴ and lipase and amylase increases have been observed previously after initiation of treatment with several DPP-4is and GLP-1RAs, including liraglutide.^{15–17} In this trial, lipase changes were observed among subjects continuing on pretrial sitagliptin and those switching to liraglutide. A non-significant, minor increase in amylase was also observed in both treatment groups. Similar increases in pulse rate with liraglutide, as reported in this trial, have been previously reported.¹⁸ While no AEs related to elevated pulse rate were reported during the trial, the clinical relevance is currently unknown. However, a cardiovascular outcomes trial (LEADER) to determine long-term effects of liraglutide on cardiovascular safety in subjects with T2D has recently been completed and showed that liraglutide significantly reduces the risk of major adverse cardiovascular events.¹⁹

This is the first trial with a robust randomized, double-blind, double-dummy, active-controlled design to address the question of whether patients with T2D insufficiently controlled on sitagliptin therapy might obtain improved glycaemic control by switching to liraglutide. Switching from sitagliptin to a GLP-1RA has been previously

assessed, but these trials have been either extension or open-label studies, or not designed as confirmatory trials.^{11,20,21} In the 26-week, open-label extension to the DURATION-2 trial, switching from sitagliptin to once-weekly exenatide resulted in significantly improved glycaemic control, as well as weight loss, but to a lesser extent than in the current LIRA-SWITCH trial.²⁰ The reduction in HbA_{1c} and body weight in the DURATION-2 trial was consistent with results from a non-inferiority trial,²¹ in which switching from sitagliptin to twice-daily exenatide significantly reduced HbA_{1c}; however, non-inferiority was not met when comparing HbA_{1c} reduction in the switch arm of this trial with HbA_{1c} reduction in the add-on exenatide arm.

Typical strategies for patients failing on OADs include adding a third OAD or adding insulin therapy.² Each of these choices will increase regimen complexity and may compromise tolerability. Therefore, switching from a DPP-4i to a GLP-1RA could be seen as a pragmatic and attractive option, which offers the benefit of allowing the patient to remain on dual therapy while still achieving a superior improvement in glycaemic control and weight loss. Thus, the effects of switching from sitagliptin to liraglutide on glycaemic control and body weight in this trial suggest that moving horizontally in the treatment algorithm^{1,2} is a relevant option that may safely be considered for subjects insufficiently controlled on sitagliptin.

The benefit observed here, when switching from a DPP-4i to liraglutide, may not necessarily be transferred to other GLP-1RAs, given that GLP-1RAs have shown different efficacy outcomes regarding glycaemic control and change in body weight.^{15,22–25} It also follows that this trial may not necessarily be extrapolated to cover switching from any DPP-4i to liraglutide.

In conclusion, results from the LIRA-SWITCH trial confirm that patients with T2D insufficiently controlled with sitagliptin who switch to liraglutide can obtain clinically relevant reductions in glycaemia and body weight, without compromising safety. This switch provides a clinically relevant option for improved T2D management while allowing patients to remain on dual therapy.

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Conflict of interest

T.S.B. received research support from Abbott, ACON, Bayer, BD, Boehringer Ingelheim, Bristol-Myers Squibb, Companion Medical, Dexcom, Elcelyx, Insulet, Janssen, Lexicon, Lifescan, Lilly, Medtronic, Merck, Novo Nordisk, Sanofi, and Versartis; received consulting honoraria from AstraZeneca, Bayer, BD, Lilly, Medtronic, Novo Nordisk, Sanofi; and received speaking honoraria from Abbott, Insulet, Novo Nordisk, and Sanofi. F.J.T. is a member of advisory boards for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Hoffman LaRoche, Merck, Merck Sharp & Dohme, Novartis, Novo Nordisk and Sanofi; is a consultant for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Hoffman LaRoche, Merck, Merck Sharp & Dohme, Novartis, Novo Nordisk, and Sanofi; and received research support from AstraZeneca, Eli Lilly, Hoffman LaRoche, Merck, Merck Sharp & Dohme, Novartis, Novo Nordisk, and Sanofi. G.M.T. is a member of advisory boards for Amgen, Merck and Eli Lilly; and received speaking honoraria from Amgen, AstraZeneca, Eli Lilly & Novo Nordisk. A.B.-T. and M.S.K. are employees of Novo Nordisk A/S. R.T., P.V.R. and M.M. have no conflicts to declare.

Author contributions

M.S.K. and A.B.T. were the medical directors for the trial. They and their teams designed the trial, developed the protocol and were responsible for trial conduct, data analysis and presentation. T.S.B., R.T., F.J.T., P.V.R., G.M.T., A.B.T., M.S.K. and M.M. contributed to data acquisition, analysis, interpretation and writing the manuscript. All authors contributed to revisions and approved the final version. T.S.B. is the guarantor and had full access to all the study data and takes responsibility for integrity of the data and accuracy of the analysis.

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SUPPORTING INFORMATION

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