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ORIGINAL ARTICLE

Efficacy and safety of liraglutide versus sitagliptin, both in combination with metformin, in Chinese patients with type 2 diabetes: a 26-week, open-label, randomized, active comparator clinical trial

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Aims: To compare the efficacy and safety of liraglutide versus sitagliptin as add-on to metformin after 26 weeks of treatment in Chinese patients with type 2 diabetes mellitus (T2DM).

Methods: This 26-week open-label, active comparator trial (NCT02008682) randomized patients (aged 18–80 years) with T2DM inadequately controlled with metformin [glycated haemoglobin (HbA1c) 7.0–10.0% (53–86 mmol/mol)] 1 : 1 to once-daily subcutaneously administered liraglutide 1.8 mg (n = 184) or once-daily oral sitagliptin 100 mg (n = 184), both as add-on to metformin. The primary endpoint was change in HbA1c from baseline to week 26.

Results: Liraglutide was superior to sitagliptin in reducing HbA1c from baseline [8.1% (65 mmol/mol)] to 26 weeks, as evidenced by estimated mean HbA1c change of −1.65% (−18.07 mmol/mol) versus −0.98% (−10.72 mmol/mol), respectively [estimated treatment difference for liraglutide vs sitagliptin of −0.67% (95% CI −0.86, −0.48) or −7.35 mmol/mol (95% CI −9.43; −5.26); $p < 0.0001$]. More patients receiving liraglutide (76.5%) than sitagliptin (52.6%) achieved the HbA1c target of <7.0% (53 mmol/mol) at week 26 [odds ratio 3.65 (95% CI 2.18, 6.12); $p < 0.0001$]. Reductions in fasting plasma glucose, 7-point self-measured plasma glucose and body weight were greater with liraglutide than with sitagliptin ($p < 0.0001$ for all). More patients experienced nausea (14.8% vs 0.5%), diarrhoea (8.2% vs 2.2%) and decreased appetite (10.9% vs 0.5%) with liraglutide than sitagliptin. Two hypoglycaemic episodes were confirmed for liraglutide and one for sitagliptin; none were severe or nocturnal.

Conclusions: Liraglutide provided better glycaemic control and greater body weight reduction than sitagliptin when administered as add-on to metformin. More patients had nausea, diarrhoea and decreased appetite with liraglutide versus sitagliptin.

Keywords: Chinese, liraglutide, sitagliptin, type 2 diabetes

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Introduction

Diabetes represents a large healthcare burden in China, with the prevalence of type 2 diabetes (T2DM) increasing from 9.7 in 2008 to 11.6% (100 million people) in 2010 [1,2]. The focus of T2DM management is to optimize glycaemic control to reduce microvascular complications [3] and potentially macrovascular outcomes [4]. Among Chinese adults with diabetes receiving treatment, only 39.7% had adequate glycaemic control [2], indicating sub-optimal antihyperglycaemic treatment. The choice of glucose-lowering regimen should be individually tailored and take into account patient characteristics such as age and comorbidities [3]. Approximately 50% of Chinese patients with T2DM are classified as overweight [body mass index (BMI) 24.0–27.9 kg/m^2) or obese (BMI ≥ 28.0 kg/m^2) [5,6]. It is well recognized that overweight and obesity are significantly associated with an increased risk of diabetes in Chinese adults [2].

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Further, weight loss is associated with improvements in clinical symptoms and cardiovascular disease risk factors in individuals with T2DM [7,8].

Liraglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA), and sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, both incretin-based therapies, are recommended in global T2DM management guidelines as second-line treatment when metformin monotherapy is insufficient to maintain glycaemic targets [3]. Sitagliptin and liraglutide have different modes of action and are, therefore, expected to have different efficacy and safety profiles. DPP-4 inhibitors prevent the proteolytic breakdown of endogenous glucagon-like peptide-1 (GLP-1), whereas GLP-1RAs mimic the effects of endogenous GLP-1 [9]. In a head-to-head clinical trial conducted in Western countries, liraglutide 1.2 and 1.8 mg were associated with significantly better glycaemic control and greater body weight reduction than sitagliptin 100 mg, both as an add-on to metformin. Compared with sitagliptin, the estimated mean treatment difference (ETD) at week 26 for glycated haemoglobin (HbA1c)-lowering and change in body weight for liraglutide 1.8 mg was −0.60% [95% confidence interval (CI) −0.77, −0.43], or −7 mmol/mol (95% CI 8, −5; $p < 0.0001$), and −2.42 kg (95% CI −3.14, −1.70; $p < 0.0001$), and for liraglutide the values were 1.2 mg −0.34% (95% CI −0.51, −0.16), or −4 mmol/mol (95% CI −6, −2; $p < 0.0001$) and −1.90 kg (95% CI −2.61, −1.18; $p < 0.0001$), respectively [10]. The superior effect of liraglutide was sustained over 1 year [11]. *Post hoc* analysis of the 26-week trial, comparing liraglutide 1.2 and 1.8 mg, showed superiority regarding change in HbA1c and statistically significant improvement in the proportion of patients reaching HbA1c targets of <7.0 and ≤6.5% (53 and 48 mmol/mol) for liraglutide 1.8 mg versus 1.2 mg [10]. Although the overall efficacy and safety/tolerability of liraglutide [12] and sitagliptin [13] have been established in Chinese patients with T2DM, there is a lack of data directly comparing the efficacy and safety of these two agents in this population.

We report the results of the LIRA-DPP-4 CHINA™ trial, which assessed the efficacy and safety of subcutaneously administered liraglutide 1.8 mg versus orally administered sitagliptin 100 mg, as add-on to metformin, in Chinese patients with T2DM.

Materials and Methods

Participants

The trial was conducted at 25 sites in China between December 2013 and November 2014. Eligible participants (aged 18–80 years) had T2DM with HbA1c 7.0–10.0% (53–86 mmol/mol) and were treated with metformin monotherapy at a stable dose of ≥1500 mg/day or maximum-tolerated dose of ≥1000 mg/day for 60 days before screening, and had a BMI ≤ 45.0 kg/m^2. Key exclusion criteria included treatment with any antihyperglycaemic agent other than metformin within 60 days before screening, history of pancreatitis, screening calcitonin value ≥50 ng/l, history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, cancer diagnosis in the previous 5 years and impaired renal or hepatic function.

This trial (NCT 02008682) complied with the Declaration of Helsinki and Good Clinical Practice guidelines [14,15]. Independent Ethics Committees approved the trial conduct. All patients gave written consent prior to trial-related activities.

Trial Design

This 26-week, open-label, active-comparator, two-armed, parallel-group, multicentre trial randomized eligible patients 1 : 1 to injectable liraglutide 1.8 mg once daily (Novo Nordisk) or oral sitagliptin 100 mg once daily (Merck), both as add-on to metformin at stable pre-trial dose. Randomization was performed using an interactive voice/web response system, with stratification by baseline HbA1c levels of 7.0–8.0% (53–64 mmol/mol) and 8.1–10.0% (65–86 mmol/mol).

The starting dose of subcutaneous liraglutide was 0.6 mg/day, with subsequent weekly escalations of 0.6 mg, according to the approved dose escalation, until the maintenance dose of 1.8 mg/day was reached [16]. In the maintenance period, the liraglutide dose could be reduced to 1.2 mg if 1.8 mg was not tolerated, and thereafter increased to 1.8 mg or remain at 1.2 mg at the investigator's discretion.

Liraglutide (once daily) injections and fixed-dose oral sitagliptin (once daily) could be administered at any time of day, irrespective of meals, but administration time was to remain consistent throughout the trial.

Metformin dose or dosing frequency was not changed during the treatment period.

After randomization, patients unable to tolerate the relevant minimum dose level (liraglutide: 1.2 mg; sitagliptin: 100 mg; metformin: unchanged dose from randomization) were discontinued from the trial product.

Endpoints

The primary endpoint was change in HbA1c from baseline to week 26. Supportive prespecified secondary endpoints included: patients achieving HbA1c <7.0% (<53 mmol/mol) and ≤6.5% (≤48 mmol/mol), patients achieving composite endpoints [HbA1c <7.0% without weight gain, HbA1c <7.0% without confirmed hypoglycaemic episodes, HbA1c <7.0% without weight gain and without confirmed hypoglycaemic episodes, HbA1c <7.0% without weight gain and systolic blood pressure (SBP) <140 mmHg], as well as fasting plasma glucose (FPG), 7-point self-measured plasma glucose (SMPG) profile, fasting lipid profiles [total cholesterol, HDL cholesterol, LDL cholesterol, very-low-density lipoprotein (VLDL) cholesterol, triglycerides and free fatty acids], body measurements (body weight, BMI, waist circumference and waist-to-hip ratio), blood pressure [SBP and diastolic blood pressure (DBP)] and patient-reported outcomes, assessed using the Diabetes Treatment Satisfaction Questionnaire (DTSQ). Safety endpoints included: confirmed hypoglycaemic episodes, adverse events (AEs), haematology and biochemistry variables (including lipase and amylase), calcitonin and resting pulse. Confirmed hypoglycaemia was defined as severe episodes (requiring third-party assistance) or biochemically confirmed by a plasma glucose value <3.1 mmol/l (56 mg/dl), with/without symptoms. Nocturnal hypoglycaemia was defined as confirmed episodes occurring between 00:01 and 05:59 am.

Statistical Analyses

Sample size was determined using the assumption of a one-sided *t*-test of size 2.5% and a zero mean treatment difference. Based on previous experience [9,11], the standard deviation of 1.1% for HbA1c was estimated, leading to the calculation that at least 137 completing patients in each treatment group were required to achieve a power of 85% to show non-inferiority of liraglutide versus sitagliptin. Based on an assumed drop-out rate of 25%, the total number of patients planned for randomization was 366, with 183 in each treatment group.

Efficacy endpoints were based on the full analysis set, which included all randomized patients who were exposed to trial products and had any post-randomization data. Safety endpoints were based on the safety analysis set, which included all patients exposed to trial products. The primary endpoint was analysed using a mixed model for repeated measurements (MMRM) with treatment and HbA1c strata as factors and baseline HbA1c as covariates. Non-inferiority would be confirmed if the upper bound of the two-sided 95% CI for the mean HbA1c treatment difference was ≤0.4% (4 mmol/mol) [17] and superiority would be confirmed if the upper limit of the 95% CI was below 0. For the secondary endpoints, continuous variables were analysed using a method similar to that used for the primary endpoint, and the dichotomous variables were analysed using a logistic regression model, with treatment and HbA1c strata as factors and baseline HbA1c as a covariate. *Post hoc* analyses of weight loss (proportion of patients losing ≥5% of baseline body weight) and composite endpoints [proportion achieving HbA1c <7.0% (<53 mmol/mol) and weight loss ≥5% without confirmed hypoglycaemia], deemed important in the Chinese guidelines on T2DM management [18], were conducted using a logistic regression model. Additionally, *post hoc* subgroup analyses were performed within treatment groups according to baseline BMI (≥28 and <28 kg/m^2) and baseline HbA1c [≤8% (≤64 mmol/mol) and >8%]. Responses by HbA1c were analysed using a MMRM, with treatment, HbA1c subgroup and treatment by HbA1c subgroup as fixed factors and baseline as a covariate, all nested within visit. Responses by BMI group had treatment, stratification groups, BMI subgroup and treatment by BMI subgroup interaction as fixed factors. Unless otherwise specified, safety endpoints were analysed using descriptive statistics only. Statistical analyses were performed using SAS software (version 9.3; SAS Institute Inc., Cary, NC, USA).

Results

Efficacy

Of 498 patients screened, 368 were randomly assigned to the treatments, with 183 patients in the liraglutide group and 184 patients in the sitagliptin group exposed to trial product. One patient in the liraglutide group withdrew before exposure and was excluded from the full analysis set (Figure 1). Baseline characteristics were well balanced between the two groups (Table 1). For the liraglutide group, 93.6% of the patients who completed the trial without discontinuation of trial product maintained the 1.8 mg dose until end of trial.

At week 26, mean reductions in HbA1c from baseline were −1.65% (−18.07 mmol/mol) for liraglutide and −0.98% (−10.72 mmol/mol) for sitagliptin (Figure 2A, B). The ETD for liraglutide versus sitagliptin was −0.67% (95% CI −0.86, −0.48), or −7.35 mmol/mol (95% CI −9.43; −5.26; $p < 0.0001$), confirming the superiority of liraglutide. More patients achieved HbA1c <7.0% (<53 mmol/mol) or ≤6.5% (≤48 mmol/mol) and the composite endpoints with liraglutide than with sitagliptin (Figure 3A).

Both treatments reduced FPG levels after 26 weeks, but reduction was greater with liraglutide (−2.39 mmol/l) than with sitagliptin (−1.17 mmol/l), resulting in an ETD at week 26 of −1.22 mmol/l (95% CI −1.63, −0.81; $p < 0.0001$) in favour of liraglutide (Figure 2C).

At week 26, the 7-point SMPG profile was improved at all seven time points for both treatments (Figure 2D). Improvements were greater with liraglutide than sitagliptin, as evidenced by the change in the mean of the SMPG profile of −2.28 mmol/l versus −1.33 mmol/l [ETD −0.95 mmol/l (95% CI −1.29, −0.61; $p < 0.0001$)].

Body weight reduction at week 26 was greater with liraglutide than with sitagliptin [−3.17 kg vs −1.08 kg, respectively; ETD −2.10 kg (95% CI −2.76, −1.43); $p < 0.0001$ (Figure 2E)]. Liraglutide was also associated with greater reductions in BMI [−1.17 kg/m^2 vs −0.40 kg/m^2; ETD −0.77 kg/m^2 (95% CI −1.00, −0.53); $p < 0.0001$] and waist circumference [−2.64 cm vs −1.11 cm, ETD −1.53 cm (95% CI −2.38, −0.67); $p = 0.0005$] (Table S1, Supporting Information). Waist-to-hip ratio was almost unchanged for both groups.

In *post hoc* analyses of additional endpoints, more liraglutide-treated patients achieved the composite endpoint of HbA1c <7.0% (<53 mmol/mol) and weight loss ≥5% without confirmed hypoglycaemia [37.0% vs 10.9%, OR 5.44 (95% CI 3.01, 9.85); $p < 0.0001$ (Figure 3B)].

Both treatments decreased SBP and DBP [SBP change −4.31 mmHg vs −2.76 mmHg and DBP change −1.37 mmHg vs −0.96 mmHg, for the liraglutide and sitagliptin groups, respectively; $p > 0.05$ for both (Table S1, Supporting Information)].

There was no statistically significant difference between the two groups for any of the lipid variables (Table S1, Supporting Information).

Results of *post hoc* subgroup analyses demonstrated statistically significant greater mean reductions in HbA1c and body weight from baseline with liraglutide versus sitagliptin, regardless of HbA1c and BMI at baseline (Table S2, Supporting Information). Patient-reported outcomes, as evaluated using the DTSQ, showed a slightly improved overall treatment satisfaction score in both treatment groups; no statistically significant difference was found between the groups [mean change from baseline 0.70 (liraglutide) vs. 0.76 (sitagliptin)].

Safety and Tolerability

Overall, both treatments were well tolerated. More patients reported AEs with liraglutide than with sitagliptin (55.7% vs 34.2%, respectively; Table 2). Serious AEs (SAEs) were

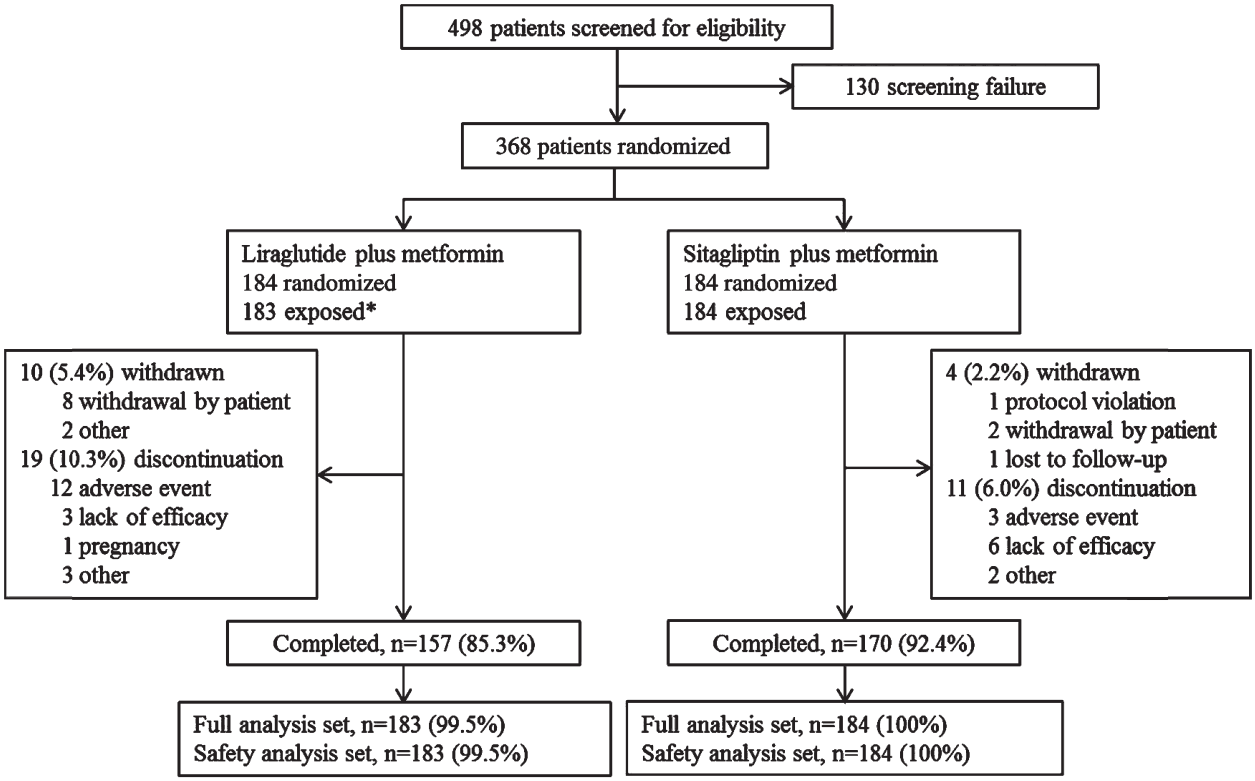

Figure 1. Patient disposition. *One patient withdrew before exposure. Discontinuation: patients stopped trial product but remained in the trial to collect end of trial safety and efficacy information. Withdrawn: patients stopped trial product and left the trial.

reported in three patients (1.6%) with liraglutide versus six patients (3.3%) with sitagliptin. SAEs showed no consistent pattern regarding system organ class or preferred terms of the events, and most SAEs in both groups occurred as single events (Table 2). Two neoplasms (thyroid cancer and malignant thymoma) were reported in the sitagliptin group. No deaths occurred during the trial. More patients were discontinued from trial product as a result of AEs with liraglutide than with sitagliptin (6.6% vs 1.6%). The proportion of patients with AEs assessed by the investigators to be possibly/probably related to trial products was higher in the liraglutide group (43.2%) versus the sitagliptin group (13.0%). AEs were mostly mild or moderate in both groups, and the majority of patients reporting AEs had recovered by end of trial. The difference in incidence of AEs was primarily attributable to more patients reporting gastrointestinal disorders and metabolism and nutrition disorders in the liraglutide group versus the sitagliptin group (Table 2). The following AEs were reported in a higher proportion of liraglutide-treated patients versus sitagliptin-treated patients: nausea (14.8% vs 0.5%), diarrhoea (8.2% vs 2.2%) and decreased appetite (10.9% vs 0.5%). Most cases of nausea and diarrhoea occurred during the initial weeks of liraglutide treatment (Figure S1, Supporting Information). Increased lipase levels were reported in 11 liraglutide-treated patients (6.0%) versus 8 sitagliptin-treated patients (4.3%).

No episodes of severe hypoglycaemia were reported. Two patients reported two episodes of confirmed hypoglycaemia (liraglutide group), and one patient reported one episode of confirmed hypoglycaemia (sitagliptin group); none of these episodes was nocturnal.

Serum amylase levels increased slightly in both groups; no statistically significant difference was found between the treatments [ratio to baseline 1.10 (liraglutide) and 1.06 (sitagliptin); estimated treatment ratio (ETR) 1.04 (95% CI

Table 1. Demographic and baseline characteristics.

	Liraglutiden = 183	Sitagliptinn = 184
Male; female, n (%)	102 (55.7); 81 (44.3)	117 (63.6); 67 (36.4)
Mean (s.d.) age, years	51.7 (10.7)	51.4 (11.0)
Mean (s.d.) body weight, kg	76.2 (13.6)	75.8 (15.1)
Mean (s.d.) BMI, kg/m^2	27.3 (3.4)	27.2 (4.0)
Mean (s.d.) duration of diabetes, years	5.3 (4.4)	5.2 (5.4)
Mean (s.d.) HbA1c, %	8.14 (0.83)	8.11 (0.78)
Mean (s.d.) HbA1c, mmol/mol	65.5 (9)	65.1 (9)
Mean (s.d.) FPG, mmol/l	9.26 (2.22)	9.46 (2.24)
Use of concomitant medications*, n (%)		
Angiotension-converting enzyme inhibitors	12 (6.6)	10 (5.4)
Angiotensin II antagonist	1 (0.5)	1 (0.5)
β-blockers	12 (6.6)	10 (5.4)
Statins	26 (14.2)	18 (9.8)

BMI, body mass index; HbA1c, glycated haemoglobin; FPG, fasting plasma glucose; s.d., standard deviation.
*Concomitant medication ongoing at screening. Data are number (% of total participants in the treatment group) for gender and use of concomitant medications, and mean (s.d) for other baseline parameters.

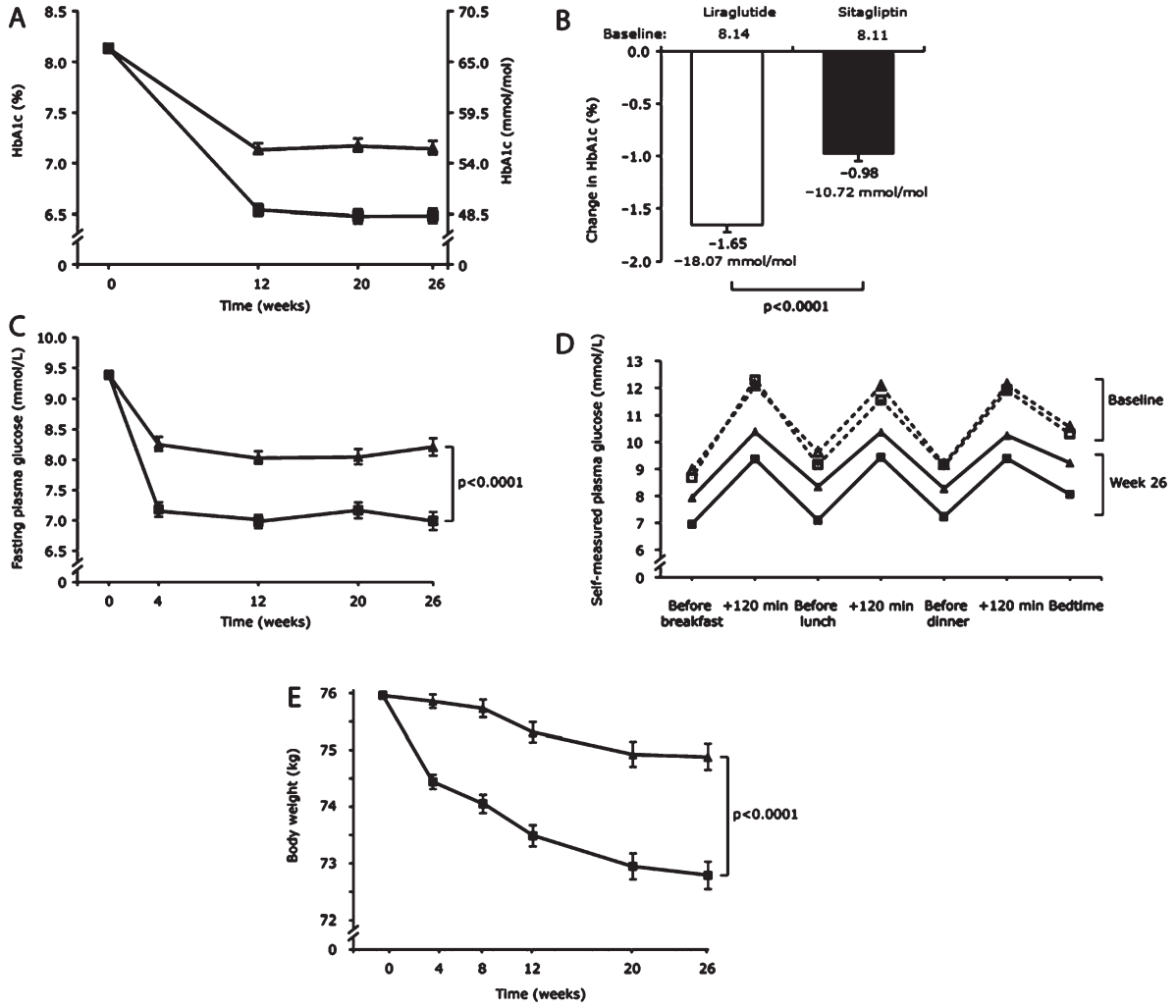

Figure 2. Efficacy endpoints from baseline to week 26. (A) HbA1c estimated means [±standard error of mean (s.e.m.)]. (B) Change in glycated haemoglobin (HbA1c). (C) Fasting plasma glucose estimated means (±s.e.m.). (D) Seven-point self-measured plasma glucose profiles. Dashed line: baseline; solid line: week 26. (E) Body weight estimated means (±s.e.m.). For (A), (C), (D) and (E): squares, liraglutide; triangles, sitagliptin.

0.98, 1.09; p = 0.1733)]. The increase in lipase levels was greater with liraglutide than sitagliptin [ratio to baseline 1.38 vs 1.17; ETR 1.19 (95% CI 1.09, 1.29); p < 0.0001 (Table S1, Supporting Information)]. No pancreatitis cases or suspicion of pancreatitis was reported. For haematology or biochemistry variables, changes from baseline to week 26 were small and no clinically relevant differences were observed between the two treatment groups. After 26 weeks, no increase in serum calcitonin level was noted with either treatment. At week 26, mean resting pulse had increased slightly from baseline with liraglutide (2.00 beats/min), but remained almost unchanged with sitagliptin (−0.38 beats/min; Table S1, Supporting Information). The treatment difference in resting pulse was statistically significant (ETD 2.37; 95% CI 0.69, 4.06; p = 0.0059).

Discussion

This head-to-head comparison of liraglutide versus sitagliptin in Chinese patients with T2DM, inadequately controlled on metformin monotherapy, was undertaken to obtain local comparative data on efficacy and safety of incretin-based therapies. Results of a meta-analysis comparing the HbA1c-lowering efficacy of GLP-1RAs between Asian and non-Asian patients with T2DM suggest that GLP-1RAs lower HbA1c to a greater extent in Asian-dominant studies than in non-Asian-dominant cohorts [19]. In contrast to the multi-ethnic populations of the Liraglutide Effect and Action in Diabetes (LEAD) one to six trials and the previous head-to-head comparison of liraglutide and sitagliptin (LIRA-DPP-4), the present trial's population was exclusively Chinese. Furthermore, at baseline, the population of this trial had lower mean HbA1c and lower mean BMI than patients treated with liraglutide 1.8 mg in the LEAD 1–6 and LIRA-DPP-4 populations at baseline [HbA1c 8.1% (65 mmol/mol) vs 8.2–8.5% (66–69 mmol/mol) and 8.4% (68 mmol/mol); BMI 27.3 kg/m^2 vs 30.0–33.5 kg/m^2 and 33.1 kg/m^2, respectively]; however, the mean duration of diabetes was within the range seen in the LEAD and LIRA-DPP-4 trials (5.3 years vs 5.3–9.2 and 6.4 years,

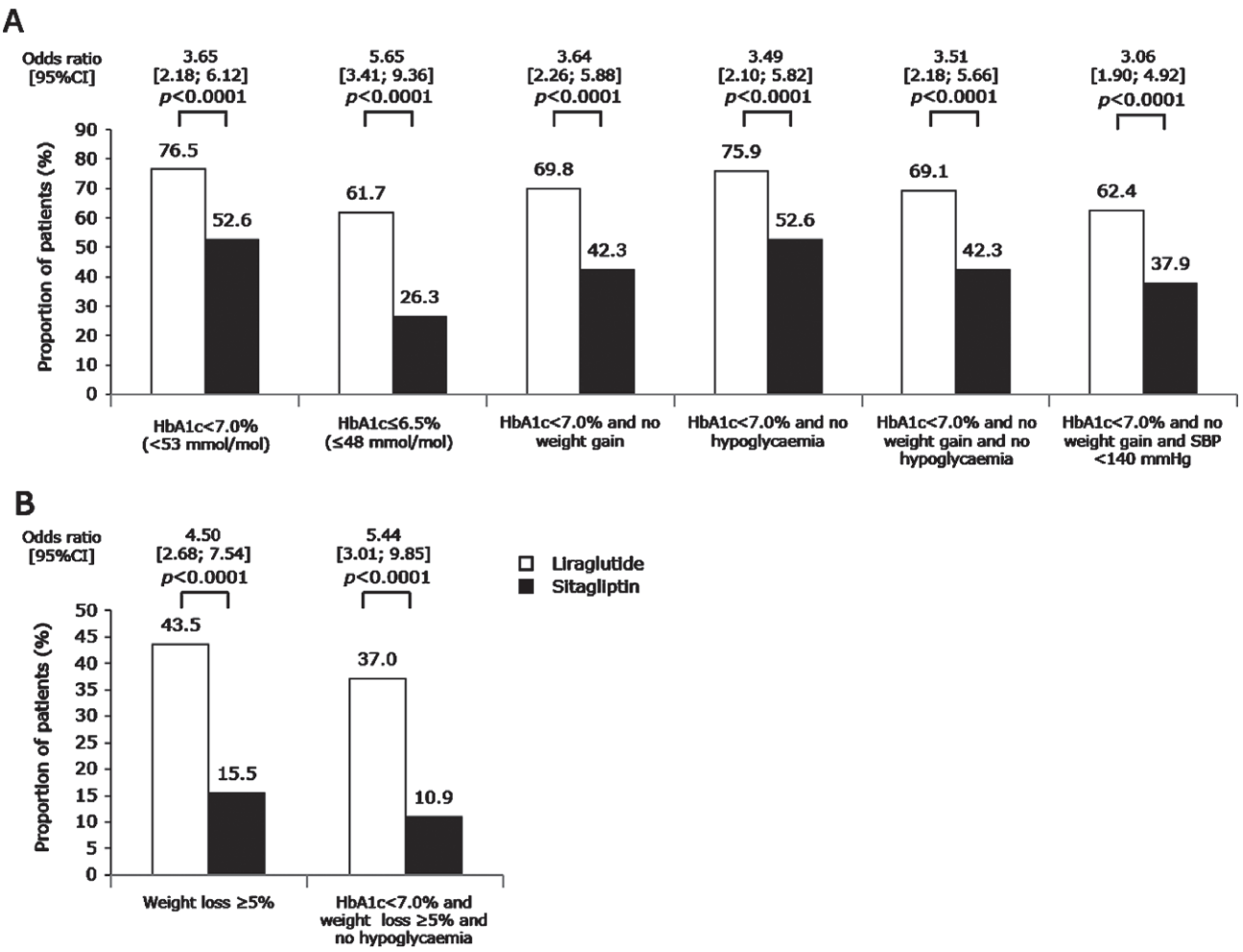

Figure 3. Proportion of patients achieving treatment targets and composite endpoints after 26 weeks of treatment. (A) Glycated haemoglobin (HbA1c) <7.0% (53 mmol/mol) and ≤6.5% (48 mmol/mol) the composite endpoints. (B) *Post hoc* weight loss ≤5% and composite endpoints. CI, confidence interval; SBP, systolic blood pressure. Hypoglycaemia refers to confirmed hypoglycaemia. p values refer to odds ratios.

respectively) [10,20–25]. In the present trial, liraglutide was associated with better glycaemic control, as evidenced by larger HbA1c reduction, greater percentage of patients reaching HbA1c targets, larger reduction in FPG and mean SMPG profile, and greater improvements in body measurements (body weight, BMI, waist circumference), compared with sitagliptin. The reductions in blood glucose and body weight observed with liraglutide or sitagliptin in the present trial were consistent with previous results observed with these agents in Chinese patients with T2DM [12,13,26,27].

The reduction of cardiovascular risk factors is an important consideration in T2DM management. In the present trial, both liraglutide and sitagliptin had a favourable effect on risk factors such as SBP and body weight, with the latter being reduced to a greater extent with liraglutide than sitagliptin. Excessive body weight and high BMI are associated with various metabolic abnormalities such as worsened insulin resistance, adding difficulties in controlling glycaemia and increasing the risk of diabetes complications [28,29]. In contrast to traditional antihyperglycaemic agents, such as insulin and sulphonylureas, liraglutide has been shown to promote weight loss, with a reduction of ~2–3 kg [12,30,31]. Weight loss in the present trial was 3.17 kg with liraglutide, and approximately half of liraglutide-treated patients lost at least 5% of their body weight.

A composite endpoint of patients achieving HbA1c <7.0% (<53 mmol/mol) without weight gain or hypoglycaemic episodes was achieved by more liraglutide-treated patients compared with the sitagliptin group. Because of the low number of confirmed hypoglycaemic events reported in this trial (liraglutide group, n = 2; sitagliptin group, n = 1), this result was largely driven by more liraglutide-treated patients achieving HbA1c <7.0% and more patients not exhibiting weight gain. Similarly, more liraglutide-treated patients reached a composite endpoint of HbA1c <7.0% and weight loss ≥5% without hypoglycaemia, compared with those treated with sitagliptin.

The improved treatment effects with liraglutide versus sitagliptin did not show any dependence on HbA1c or BMI subgroup ($p > 0.05$), as demonstrated by *post hoc* subgroup analyses.

Overall, both liraglutide and sitagliptin were well tolerated. Consistent with previous studies, the most commonly reported AEs, which were more frequent in liraglutide-treated

Table 2. Treatment-emergent adverse events.

	Liraglutiden = 183	Sitagliptinn = 184
Overall, n (%)	102 (55.7)	63 (34.2)
Serious adverse events, n (%)		
Overall	3 (1.6)	6 (3.3)
Gastric ulcer	0	1 (0.5)
Haemorrhoids	0	1 (0.5)
Thyroid cancer	0	1 (0.5)
Thymoma malignant	0	1 (0.5)
Atrial fibrillation	0	1 (0.5)
Sudden hearing loss	1 (0.5)	0
Bronchitis	1 (0.5)	0
Diabetic ketoacidosis	1 (0.5)	0
Cerebral infarction	0	1 (0.5)
Adverse events in ≥5% patients, n (%)		
Gastrointestinal disorders		
Nausea	27 (14.8)	1 (0.5)
Diarrhoea	15 (8.2)	4 (2.2)
Metabolism and nutrition disorders, n (%)		
Decreased appetite	20 (10.9)	1 (0.5)
Investigations		
Increased lipase	11 (6.0)	8 (4.3)

patients, were gastrointestinal disorders [20–25] (nausea and diarrhoea), as well as metabolism and nutrition disorders (decreased appetite). Gastrointestinal AEs are a known side effect of GLP-1RAs and are typically mild and transient, disappearing after the initial few weeks to month of treatment [32] and are mitigated by stepwise dose escalation, as indicated in the labelling [16]. Occurrence of hypoglycaemia was low in the present trial, in line with the glucose-dependent mechanism of action of both GLP-1RAs and DPP-4 inhibitors [9]. As previously reported with liraglutide and other GLP-1RAs [10,33–35], liraglutide treatment resulted in an increased resting pulse in patients in the present trial. Although the clinical relevance of this is unclear, results from localization studies suggest the mechanism may be partly explained by GLP-1-mediated stimulation of GLP-1 receptor on sinoatrial myocytes [36]. The ongoing cardiovascular outcomes trial (LEADER) is evaluating the long-term effects of liraglutide on cardiovascular safety in patients with T2DM at high risk of cardiovascular disease [37].

Up to 25% of patients with T2DM have elevated serum amylase or lipase [38]. Additionally, incretin-based therapies have been associated with increased serum amylase or lipase [35,38–40]. The clinical mechanism by which this increase occurs is unknown. In the present trial, there was a greater serum lipase increase in liraglutide-treated patients than in sitagliptin-treated patients. No pancreatitis or suspicion of pancreatitis was observed here, consistent with previous findings that increased lipase levels are not indicative of pancreatitis [38].

In the present trial, patients were allowed to reduce the liraglutide dose from 1.8 to 1.2 mg if required to because of tolerability issues; however, 93.6% of liraglutide-treated patients completed the trial on the 1.8 mg/day dose. The efficacy achieved in the present trial is consistent with that previously reported for liraglutide 1.8 mg/day [10] and no new safety signals were encountered, thereby confirming the documented favourable risk–benefit profile of liraglutide 1.8 mg/day for treatment of T2DM in Chinese patients [12].

The open-label trial design was considered a limitation that may introduce bias. Furthermore, although the 26-week treatment duration was considered sufficient to assess changes in glycaemic control variables, it was not sufficient to assess whether the observed cardiometabolic improvements could be maintained in the long term. However, as the results in this trial were similar to those conducted in Western populations [10], a similar long-term effect could be expected. While adequate glycaemic control may be achieved with 1.2 mg liraglutide [20–23], the majority (93.6%) of patients in the liraglutide arm of this trial were treated with 1.8 mg liraglutide; this may be considered a limitation of the trial.

Liraglutide and sitagliptin are both recommended as possible second-line treatment options for the management of hyperglycaemia in T2DM after metformin failure by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) [3]. Sitagliptin is also recommended by the Chinese Diabetes Society as a second-line treatment, in accordance with its labelling in China; however, GLP-1RAs are only recommended as third-line therapy in the Chinese guideline for treatment of T2DM [18], partially because of a paucity of data in Chinese patients [41]. In line with the ADA/EASD recommendation, the results from the present trial suggest that liraglutide might be used as a second-line treatment, providing good glycaemic control and body weight reduction, and being a generally well-tolerated treatment option in Chinese patients.

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Conflict of Interest

H. B.-T. and Y. S. are Novo Nordisk employees. Y. M. has received lecture fees and research funding from Sanofi, Novo Nordisk, Eli Lilly, Novartis and Bayer. The other authors declare no conflicts of interests.

The study sponsor participated in the study design, data collection, review and analysis.

All authors were involved in the trial operation, data collection, and preparation, review and final approval of the manuscript.

Supporting Information

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

Table S1. Changes in the secondary endpoints.

Table S2. Change from baseline glycated haemoglobin (HbA1c) and body weight by body mass index and HbA1c groups.

Figure S1. Proportion of patients with nausea by time.

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