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ORIGINAL ARTICLE

Effects of liraglutide on gallbladder emptying: A randomized, placebo-controlled trial in adults with overweight or obesity

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Aims: Treatment with liraglutide 3.0 mg has been associated with gallbladder-related adverse events. To conduct a single-centre, double-blind, 12-week trial comparing the effect of 0.6 mg liraglutide and steady-state liraglutide 3.0 mg with placebo on gallbladder emptying in adults with body mass index (BMI) ≥27 kg/m^2 and without diabetes.

Methods: Participants were randomized 1:1 to once-daily subcutaneous liraglutide (n = 26) or placebo (n = 26), starting at 0.6 mg with 0.6-mg weekly increments to 3.0 mg, with nutritional and physical activity counselling. A 600-kcal (23.7 g fat) liquid meal test was performed at baseline, after the first dose and after 12 weeks. The primary endpoint was the 12-week maximum postprandial gallbladder ejection fraction ($GBEF_{max}$), measured over 240 minutes after starting the meal.

Results: Baseline characteristics were similar between groups (mean ± SD overall age 47.6 ± 10.0 years, BMI 32.6 ±3.4 kg/m^2, 50% women). Mean 12-week $GBEF_{max}$ (treatment difference −3.7%, 95% confidence interval [CI] −13.1, 5.7) and area under the GBEF curve in the first 60 minutes (−390% × min, 95% CI −919, 140) did not differ for liraglutide 3.0 mg (n = 23) vs placebo (n = 24). The median (range) time to $GBEF_{max}$ was 151 (11-240) minutes with liraglutide 3.0 mg and 77 (22-212) minutes with placebo. Similar findings were noted after the first 0.6-mg liraglutide dose. Gastrointestinal disorders, notably nausea and constipation, were the most frequently reported adverse events.

Conclusions: Treatment with liraglutide did not affect the $GBEF_{max}$ but appeared to prolong the time to $GBEF_{max}$.

KEYWORDS

antiobesity drug, clinical trial, GLP-1, GLP-1 analogue, liraglutide, obesity therapy

1 | INTRODUCTION

Liraglutide is an analogue of the human gut incretin hormone, glucagon-like peptide 1 (GLP-1), and belongs to the class of GLP-1 receptor agonists (GLP-1RAs). GLP-1, predominantly secreted by intestinal L cells in response to food intake,[1,2] stimulates insulin secretion and inhibits glucagon secretion in a glucose-dependent manner,[1] and is known to be a physiological regulator of appetite.[3] Liraglutide promotes weight loss through reduced appetite and energy intake.[4] As an adjunct to a reduced-calorie diet and increased physical activity, liraglutide is approved at a dose of 3.0 mg for chronic weight management in adults with obesity or overweight in the presence of a weight-related comorbidity.

In the weight management clinical development programme, treatment with liraglutide 3.0 mg was associated with a greater

frequency of gallbladder-related adverse events (predominantly cholelithiasis and cholecystitis) than treatment with placebo.[5–8] In the largest phase III trial, Satiety and Clinical Adiposity – Liraglutide Evidence (SCALE) Obesity and Prediabetes, the proportion of participants reporting gallbladder-related events after 56 weeks was 2.5% (3.1 events per 100 person-years of exposure) in the liraglutide group vs 1.0% (1.4 events per 100 person-years) in the placebo group.[6] Participants experiencing such events generally had above-average weight loss,[6] consistent with the known risk of gallstones associated with weight loss[9]; however, in the 3-year part of the trial, most weight loss was observed during the first ~40 weeks of treatment, whereas the incidence of gallbladder-related events remained relatively constant over 160 weeks.[5] Likewise, in the more recently published LEADER trial, in which a mean weight loss of 2.3 kg greater than placebo was noted with liraglutide 1.8 mg after 3 years of treatment, an imbalance in gallbladder-related adverse events was also observed.[10] This discrepancy suggests that other mechanisms besides weight loss may be involved.

An increased risk of cholelithiasis has been reported with GLP-1RAs generally.[11,12] Since these drugs have been shown to reduce gastrointestinal motility,[13] it has been suggested that GLP-1RAs may also reduce gallbladder contraction and emptying.[12] In a previous trial, a single dose of exenatide reduced cholecystokinin (CCK)-stimulated gallbladder emptying, in terms of the mean maximum gallbladder ejection fraction ($GBEF_{max}$), by ~40% vs placebo in healthy individuals[14]; the mean $GBEF_{max}$ was 28.8% with exenatide vs 46.1% with placebo (estimated treatment difference −17.3%). Chronic use of GLP-1RAs could lead to impaired gallbladder contraction, resulting in the development of biliary sludge and gallstone formation and, consequently, an increased risk of cholelithiasis and cholecystitis.[12,14]

The acute effect of liraglutide 0.6 mg and chronic effects of liraglutide 3.0 mg on gallbladder emptying have not previously been investigated. The primary objective of the present randomized, double-blind trial, therefore, was to compare the effect of the first 0.6-mg dose of liraglutide and steady-state liraglutide 3.0 mg (after 12 weeks of treatment) vs placebo on postprandial gallbladder emptying stimulated by a liquid meal. The trial population comprised adults with overweight or obesity without diabetes.

2 | PARTICIPANTS AND METHODS

2.1 | Trial design

The trial was conducted at a single clinical research centre in Denmark in accordance with the Declaration of Helsinki[15] and Good Clinical Practice guidelines,[16] and was registered at ClinicalTrials.gov (identifier NCT02717858). The protocol was approved by the local health authority and independent ethics committee, and participants provided written informed consent before trial commencement.

Participants received treatment with once-daily subcutaneous liraglutide or placebo, as an adjunct to nutritional and physical activity counselling, starting at 0.6 mg and with 0.6-mg weekly increments to 3.0 mg (Figure 1). A 5% minimum weight-loss target was set, with the aim of achieving similar weight losses in each group. To stimulate gallbladder emptying, a liquid meal test (600 kcal, 23.7 g fat) was performed at baseline, after the first 0.6-mg dose and after 12 weeks, and was considered to be a suitable physiological stimulus.[17] Gastric emptying was also assessed in the 4-hour postprandial period of the meal test using the paracetamol absorption technique.[18]

2.2 | Participants

Men or women aged between 18 and 64 years (inclusive), with a body mass index (BMI) ≥27.0 kg/m^2, stable body weight (<3 kg self-reported change during the previous 90 days), and an ultrasound assessment of gallbladder volume of acceptable quality (investigator judgment) at screening were included in the trial. Key exclusion criteria were: a history of gastrointestinal surgery or other medical procedures precluding a gallbladder emptying assessment (appendectomy was allowed) or any significant digestive disease (investigator judgement); a diagnosis of type 1 or 2 diabetes mellitus; a history of pancreatitis (acute or chronic) or any gallbladder disease (cholelithiasis, gallbladder sludge, polyps); or pregnancy, breast-feeding and inadequate contraception use. Full enrolment criteria and exclusion criteria associated with the meal test are included in Tables S1 and S2 (Supporting Information).

2.3 | Treatment and randomization

Eligible participants were randomized 1:1 to liraglutide (n = 26) or placebo (n = 26; Figure 1). Randomization codes were sent by the sponsor to the site in sealed units. Liraglutide and placebo were provided in pre-filled pen-injectors (Novo Nordisk A/S, Bagsværd, Denmark). As female hormones can influence gallbladder emptying,[19] randomization was stratified by sex. The sponsor, participants and investigators remained blinded to treatment allocation.

2.4 | Counselling in healthy nutrition and physical activity

During the treatment period, trial participants received five individualized counselling sessions on nutrition and physical activity from a certified dietician, with a target weight loss of ≥5% of their initial body weight over the 12-week treatment period. Participants were advised to follow a hypocaloric diet throughout the treatment period, containing a maximum 30% of energy from fat (maximum 10% energy from saturated fats), and ~20% from protein and ~50% from carbohydrates, with an energy deficit of 500 kcal/d compared with the participant's estimated total energy expenditure. If participants were unable to lose weight after 4 weeks of treatment, more intense counselling was provided and recalculation of the recommended energy intake was allowed to obtain a greater energy deficit than the original hypocaloric diet. Participants who did not achieve the 5% weight-loss target were still included in the data analyses.

Adherence to the recommended diet was at the dietician's discretion. Increased physical activity was encouraged, with a goal of 60 minutes of moderate- to high-intensity physical activity per day and a recommended >150 minutes of moderate-intensity physical activity per week.[20]

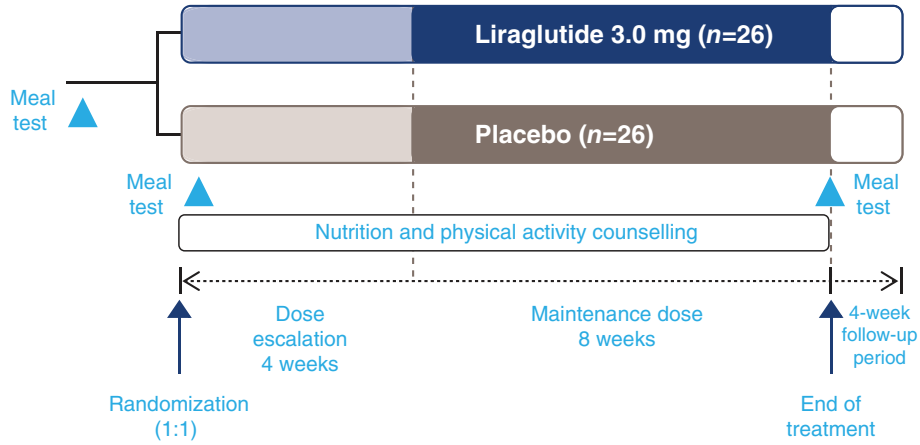

FIGURE 1 Trial design. Daily dosing started at 0.6 mg of treatment followed by dose escalation of 0.6 mg weekly increments to 3.0 mg. The meal tests took place at baseline and on days 2 and 85. Screening took place 2 to 28 days before the first meal test

2.5 | Endpoints

During each of the three meal tests, gallbladder volume was measured by ultrasonography in the fasted state and throughout the 240-minute period after the start of the meal, at 14 predefined time points. Gallbladder motility endpoints were derived from the gallbladder volume–time curves over the 240-minute period, at baseline, after the first 0.6-mg liraglutide dose and at steady-state liraglutide 3.0 mg after 12 weeks. The primary endpoint was $GBEF_{max}$ after 12 weeks. Secondary endpoints related to gallbladder motility comprised: $GBEF_{max}$ after the first 0.6-mg dose; fasting gallbladder volume; area under the GBEF–time curve 0 to 60 minutes after the start of the meal (GBEF $AUC_{0\text{-}60\ min}$); time to $GBEF_{max}$ (t_{max}); and time from t_{max} to when the gallbladder had reverted to the fasting volume after the 0.6-mg dose and at steady-state after 12 weeks of treatment.

Gastric emptying endpoints were derived from the paracetamol concentration–time curves over the same period and for the same doses as described above: paracetamol $AUC_{0\text{-}240\ min}$ and $AUC_{0\text{-}60\ min}$; maximum paracetamol concentration (C_{max}); and paracetamol t_{max}.

Other endpoints included change from week 0 to week 12 in body weight and secondary safety endpoints, comprising adverse events and changes from screening to week 12 in haematology, biochemistry, including fasting lipase and amylase, calcitonin, vital signs and physical examination. Adverse events of special medical interest (acute gallstone disease, neoplasm and pancreatitis) had additional data collection.

The timing of assessments is described in the Supplemental Methods (Supporting Information).

2.6 | Estimation of gallbladder volume

Gallbladder volume during meal tests was calculated by the ellipsoid method via ultrasound assessment of longitudinal and cross-sectional diameters[21] by a maximum of two investigators; an intra- and inter-observer variation of <10% with respect to gallbladder volume was achieved. Participants were in a supine position during the assessment. The gallbladder was measured in three dimensions: one longitudinal (D1) and two cross-sectional diameters (D2 and D3) for calculating the volume using the formula "volume = $\pi/6 \times D1 \times D2 \times D3$".[22] Fasting gallbladder volume was estimated based on the average of two sequential measurements.

2.7 | Meal test and gastric emptying

At baseline, after the first 0.6-mg dose and after 12 weeks, a 4-hour meal test was performed in the morning after an overnight fast. The liquid meal (250 mL of nutritional supplement drink [Nutridrink Compact; Nutricia AB, Allerød, Denmark]) had a total energy content of ~600 kcal and a macronutrient composition of 35% energy from fat (23.7 g), 16% from protein and 49% from carbohydrate.

Paracetamol (1500 mg, three effervescent 500 mg tablets) was dissolved in 50 mL sterile water and mixed into the liquid meal (final volume ~300 mL/340 g) for measurement of gastric emptying.[23,24] The liquid meal was ingested within 10 minutes, and consumption time standardized between meals. Before the start of the meal and for 240 minutes postprandially, the gallbladder volume was assessed and blood samples were taken at nine predefined timepoints for the measurement of paracetamol (Supplemental Methods [Supporting Information]).

2.8 | Statistical analyses

The sample size was based on the expected precision of the estimated difference in the primary endpoint (12-week $GBEF_{max}$) between the two treatment groups using a two-sided 95% confidence interval (CI) derived from the t-distribution. Based on data from a previous study,[22] the SD value for the $GBEF_{max}$ following a liquid meal was calculated to be 11%, with a mean $GBEF_{max}$ of 71%. With 40 completing participants in the trial and an SD of 12%, there was a probability of ≥80% for achieving a 95% CI for the true treatment difference of $GBEF_{max}$ within [d − 8.4%; d + 8.4%], where d is the estimated treatment difference. The results were considered sufficiently precise to evaluate the primary objective. To account for participants discontinuing, it was planned to include 48 participants in the trial to ensure that 40 completed (assuming a drop-out rate of 20%).

All analyses were carried out on randomized individuals receiving at least one treatment dose. The GBEF values were, for each timepoint, calculated from the gallbladder volume (as change from the

fasting gallbladder volume) as: GBEF(t) = 100% × [$vol_{fasting}$ − vol(t)]/$vol_{fasting}$, where $vol_{fasting}$ was the mean of two gallbladder volume assessments measured within 15 minutes before the meal, and vol(t) was the gallbladder volume measured at each timepoint, t. The primary endpoint was analysed using a linear normal model, which included treatment and sex as factors, and baseline body weight and baseline $GBEF_{max}$ as covariates. There was no imputation for missing data.

Additional gallbladder-related and gastric emptying endpoints were analysed in the same way as the primary endpoint, using the corresponding baseline value as a covariate in the model, except that the time to $GBEF_{max}$ was summarized using descriptive statistics. Gastric emptying endpoints were log transformed for analysis. AUCs were calculated using the linear trapezoidal method. Body weight and safety endpoints were summarized using descriptive statistics. Additional prespecified and exploratory analyses are described in the Supplemental Methods (Supporting Information). The statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

3 | RESULTS

3.1 | Participant characteristics

A total of 90 individuals were screened for eligibility, of which 34 were screening failures. Four individuals were withdrawn prior to randomization, 2 because of protocol violations and 2 because of cholelithiasis events, as per exclusion criteria, that were discovered by ultrasonography before the start of the meal test. All 52 randomized individuals were exposed to the trial drug; 5 were withdrawn after randomization, and 47 completed the trial. In the liraglutide group, 1 withdrawal was attributable to protocol violation and 2 participants withdrew of their own accord; in the placebo group, 1 withdrawal was attributable to an adverse event (migraine) and 1 was attributable to protocol violation. All withdrawn individuals attended the follow-up visit. The trial was conducted between March 16, 2016 and February 27, 2017.

Baseline characteristics of the trial participants were similar between treatment groups (Table 1).

3.2 | Gallbladder motility

Figure 2 shows mean gallbladder volume (A) and ejection fraction (B) profiles from 0 to 240 minutes after the start of the liquid meal at baseline (before treatment initiation), after the first 0.6-mg dose, and after 12 weeks of treatment. In each case, the gallbladder volume decreased after meal ingestion (Figure 2A and Figure S1, Supporting Information), and, accordingly, GBEF increased in both groups (Figure 2B). After the first 0.6-mg dose, the mean GBEF was higher with liraglutide than with placebo from time ~100 to ~240 minutes and remained higher with steady-state liraglutide 3.0 mg from ~150 to ~240 minutes (Figure 2B).

After 12 weeks, the estimated mean $GBEF_{max}$ (primary endpoint) did not differ for liraglutide 3.0 mg vs placebo (Table 2). Neither was any treatment difference observed in the estimated mean $GBEF_{max}$ after the first liraglutide 0.6-mg treatment dose. The $AUC_{0\text{-}60\ min}$ and fasting gallbladder volume did not differ for liraglutide vs placebo either after the first 0.6-mg dose or with liraglutide 3.0 mg after 12 weeks of treatment. The median GBEF t_{max} (time to reach maximum gallbladder contraction) at baseline was 77 minutes in the liraglutide group vs 67 minutes in the placebo group. The median (range) t_{max} increased to 104 (21-240) minutes after the first liraglutide 0.6 mg dose vs 77 (0-183) minutes with placebo and to 151 (11-240) minutes vs 77 (22-212) minutes at steady-state (no statistical testing was done). There was a wide variation in individual GBEF t_{max} values (Figure S2, Supporting Information). More than half of the GBEF profiles did not return to fasting levels within the 240-minute period (baseline: 27/52 = 52%; single dose: 33/51 = 65%; steady-state: 29/47 = 62%); therefore, the time from t_{max} to the time of the gallbladder reverting to the fasting volume was not further analysed.

TABLE 1 Baseline demographics

Characteristic	Liraglutide 3.0 mg (*n* = 26)	Placebo (*n* = 26)	Total (*n* = 52)
Women, *n* (%)	13 (50.0)	13 (50.0)	26 (50.0)
Age, years	47.6 (10.4)	47.5 (9.7)	47.6 (10.0)
Body weight, kg	98.2 (17.0)	99.8 (14.7)	99.0 (15.7)
BMI, kg/m^2	32.5 (3.6)	32.6 (3.3)	32.6 (3.4)

Abbreviations: BMI, body mass index; *n*, number of randomized participants. Data are observed means (SD), unless otherwise stated.

3.3 | Gastric emptying

Gastric emptying was slowed after the first 0.6-mg dose of liraglutide as compared with placebo, as indicated by significant reductions in the paracetamol C_{max} and $AUC_{0\text{-}240\ min}$ with liraglutide, but no treatment effect was seen with liraglutide 3.0 mg at week 12 (Table S3, Supporting Information). There were no observed treatment effects on paracetamol t_{max} after the first 0.6-mg dose or at steady state (Table S3, Supporting Information). There was no apparent relationship between the change in gastric emptying in the first hour of the meal test and the change in the time to $GBEF_{max}$ after the first 0.6-mg dose or with liraglutide 3.0 mg after 12 weeks (Table S3, Supporting Information).

3.4 | Body weight

The mean (SD) percent body weight loss after 12 weeks of treatment was 8.2 (1.8)% in the liraglutide 3.0 mg group vs 5.5 (3.6)% in the placebo group, equivalent to −7.9 (2.1) kg vs −5.5 (3.5) kg. All participants that completed the trial in the liraglutide group, as well as 13/24 participants (54%) of those in the placebo group, achieved the weight-loss goal of ≥5%. Individual changes in body weight over 12 weeks are shown in Figure S4 (Supporting Information). There was no apparent relationship between the relative change in the time to $GBEF_{max}$ and the relative change in body weight from baseline to week 12 (Figure S5, Supporting Information).

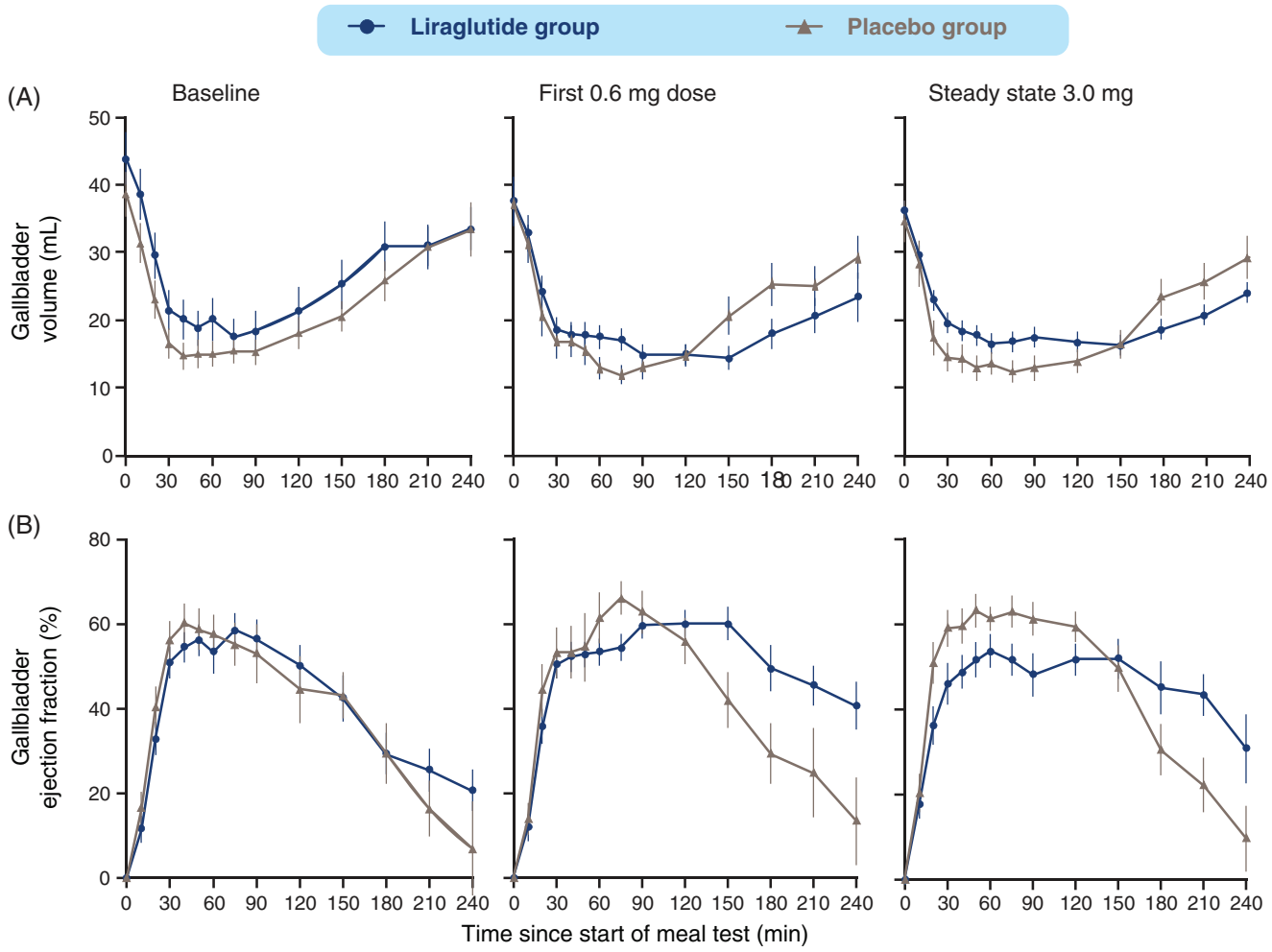

FIGURE 2 A, Gallbladder volume and B, ejection fraction profiles. Data are observed means, and error bars represent the standard error of the mean. The gallbladder ejection fraction (GBEF) values were, for each timepoint, calculated from the gallbladder volume (as change from the fasting gallbladder volume) as: GBEF(t) = 100% × ($vol_{fasting}$ − vol(t))/$vol_{fasting}$, where t = time and vol = volume

3.5 | Safety

There were no unexpected safety findings in the present trial and no new safety concerns were raised. Overall, 138 adverse events were reported by 25 participants (96.2%) in the liraglutide group as compared with 62 events by 24 participants (92.3%) in the placebo group. Most of the events were mild in severity (117 of the 138 events [85%] in the liraglutide group and 46 of the 62 events [74%] in the placebo group). As in other trials with liraglutide, the most frequently reported adverse events were gastrointestinal disorders, with nausea and constipation being the most commonly reported events. Overall, 23 participants (88.5%) in the liraglutide group reported 71 gastrointestinal events and 9 participants (34.6%) in the placebo group reported 15 events.

One serious adverse event (lower limb fracture) was reported by a participant in the placebo group during the follow-up period. One non-serious, non-symptomatic cholelithiasis event was reported in the liraglutide group. The event was discovered with ultrasonography

TABLE 2 Statistical analysis of gallbladder-related endpoints

Gallbladder-related endpoints	Liraglutide 0.6 mg *n* = 26	Placebo *n* = 25	Estimated treatment difference (95% CI)
$GBEF_{max}$, %	71.0	72.5	−1.5 (−11.4; 8.5)
GBEF $AUC_{0\text{-}60\ min}$, % × min	2309	2460	−150 (−814; 514)
Fasting volume, mL	36.5	38.6	−2.1 (−8.5; 4.4)
	Liraglutide 3.0 mg *n* = 23	**Placebo *n* = 24**	**Estimated treatment difference (95% CI)**
$GBEF_{max}$ (primary endpoint), %	70.5	74.2	−3.7 (−13.1; 5.7)
GBEF $AUC_{0\text{-}60\ min}$, % × min	2339	2729	−390 (−919; 140)
Fasting volume, mL	35.7	35.0	0.7 (−7.1; 8.5)

Abbreviations: AUC, area under the concentration–time curve; CI, confidence interval; GBEF, gallbladder ejection fraction; *n*, number of participants included in the analysis. Data are estimated means and treatment differences.

during the end-of-trial meal test assessment, 12 weeks after start of treatment. No individuals in the liraglutide group discontinued the trial as a result of adverse events vs one individual in the placebo group who discontinued because of a worsening of migraine event 14 days after starting treatment. No pancreatitis or neoplasm events were reported. No clinically relevant safety findings were identified in haematological or biochemical variables.

4 | DISCUSSION

This study evaluated the acute effects of a 0.6-mg liraglutide dose and the effects with steady-state liraglutide 3.0 mg after 12 weeks of treatment compared with placebo on postprandial gallbladder emptying after a fatty liquid meal. No effects on fasting gallbladder volume, the estimated $GBEF_{max}$ or the GBEF $AUC_{0\text{-}60\ min}$ were observed after the first 0.6-mg dose or at steady-state with liraglutide 3.0 mg, whereas the time to reach the maximum GBEF appeared to be later with liraglutide than with placebo. No significant differences in the gallbladder emptying findings were found after adjusting for weight loss or gastric emptying in the first postprandial hour, indicating that changes in these factors did not alter the trial conclusions.

The finding of no effect on the maximum gallbladder contraction with liraglutide in the present trial in adults with overweight or obesity was in contrast to results from some previous GLP-1RA trials. Reduction in CCK-induced gallbladder emptying, as observed in healthy individuals after a single dose of exenatide,[14] was likewise observed after treatment with both lixisenatide and albiglutide using similar study designs[25,26]; however, in a previous 12-week trial with liraglutide in participants with type 2 diabetes using a solid meal as stimulus for gallbladder emptying, a similar lack of treatment effect on $GBEF_{max}$ to that observed in the present trial was noted.[27] The discrepancy between trials may partly be explained by the use of a meal to stimulate gallbladder emptying in the trials in which no treatment effect was observed as compared with the use of CCK in the other trials. Although CCK has an important role in the regulation of gallbladder motility, several other neuroendocrine mechanisms are also involved, and thus the meal is thought to be a more appropriate physiological stimulus of gallbladder contraction. Differences in study populations might also have influenced the results. Some studies have indicated that the rate of gallbladder emptying is impaired in individuals with type 2 diabetes compared with healthy volunteers,[28,29] as well as in obese individuals compared with those of average BMI.[30,31] Female hormones and ageing may also impair gallbladder function.[19,32,33] The GLP-1RA treatment dose (single or multiple doses) could also have an effect, whereby tachyphylaxis of effects on gallbladder motility, as seen with gastric emptying, may occur with a long-acting GLP-1RA such as liraglutide, but not with short-acting GLP-1RAs such as exenatide.[27,29–31,34]

In the present study, we did not observe an effect of liraglutide on $GBEF_{max}$ either after 12 weeks of treatment or after the first dose of 0.6 mg, suggesting that the increased rate of gallbladder-related adverse events, such as cholelithiasis, reported with liraglutide 1.8 and 3.0 mg treatment is unlikely to have been mediated by a reduced maximum contraction of the gallbladder.[5–8,10] The data suggest, however, that the time to reach the maximum gallbladder contraction was delayed with liraglutide treatment, indicating some effect on gallbladder motility. While the clinical significance of these findings is unknown, some studies have suggested that slower ejection rates are associated with a higher risk of the development of gallstones.[12,35] The causes of gallstone formation, however, are multifactorial and also include changes in bile composition, whereby alterations in bile salts and cholesterol can promote gallstone formation.[36,37]

As weight loss is known to influence gallbladder emptying,[38] a weight loss of ≥5% at week 12 was targeted in both groups through individualized counselling sessions. Both treatment groups achieved the mean weight loss target; however, weight loss was greater in participants treated with liraglutide compared with placebo (8.2% vs 5.5%, respectively). The observed delay in the time to reach the maximum gallbladder contraction was nevertheless not associated with weight loss.

The slower rate of gastric emptying observed in the present trial after the first 0.6-mg dose of liraglutide as compared with placebo was not observed with steady-state liraglutide 3.0 mg after 12 weeks, indicating tachyphylaxis. Such an effect was previously described for GLP-1 by Nauck et al[34] and confirmed by another group with a prolonged infusion of GLP-1.[39] A recent trial with liraglutide 3.0 mg investigating gastric emptying after a solid meal assessed by scintigraphy also demonstrated tachyphylaxis of liraglutide effects after 16 vs 5 weeks, although a delay in gastric emptying compared with placebo still remained after 16 weeks.[40] In the present study, changes in gallbladder motility were not associated with changes in gastric emptying.

No unexpected safety concerns were raised in the present trial. As observed in other trials with liraglutide,[5,41] gastrointestinal disorders were the most commonly reported side effects.

A potential limitation of the present study is that the meal test duration did not capture the full refilling of the gallbladder. It was not possible to determine the full effect of liraglutide on gallbladder refilling, as many of the profiles did not return to fasting levels within the 240 minutes of the meal test. Likewise, we can only speculate as to the effects that different meals, in particular less fatty meals, might have had on gallbladder motility. Numerous hormonal interactions occur after ingestion of a high-fat meal,[27,42] which may be attenuated with less fatty meals. Nevertheless, the meal test used in the present study was considered a more appropriate physiological stimulus than the use of CCK infusion to stimulate gallbladder emptying. We used the paracetamol absorption technique for assessing gastric emptying in the present study, which could be considered a limitation as this method primarily measures the gastric emptying of fluids. It was not possible to use scintigraphy together with the meal test because of the multiple ultrasound evaluations of the gallbladder; therefore, we found the paracetamol absorption test more suitable.

In conclusion, treatment with 0.6 mg liraglutide or steady-state liraglutide 3.0 mg did not affect the maximum postprandial GBEF in this trial, but appeared to prolong the time to reach this compared with placebo treatment, indicating some effect on gallbladder motility. No unexpected safety concerns were identified.

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Conflict of interest

H.H., M.A. and L.N.G. are employed by Novo Nordisk and H.H. and L.N.G. hold stock in the company. C.C.N., P.H.S., M.B., A.B., D.P.S., L.V. and T.V. have no conflicts of interest to disclose. Within the past 36 months, F.K.K. has served on scientific advisory panels and/or speaker's bureaus for, served as a consultant to and/or received research support from Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Norgine, Novo Nordisk, Sanofi and Zealand Pharma.

Author contributions

H.H., A.B., D.P.S. and F.K.K. made substantial contributions to the conception and design of the trial, and H.H., A.B., F.K.K. and L.V. contributed to the data acquisition and data analysis. C.C.N., P.H.S., M.B., A.B. and F.K.K. made a substantial contribution to the acquisition of data. M.A., L.N.G., A.B., D.P.S, F.K.K. and L.V. made a substantial contribution to the analysis of data. All authors contributed to the interpretation of the data. All authors were involved in the writing, reviewing and editing of the manuscript, gave final approval and agreed to be accountable for all aspects of the work.

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SUPPORTING INFORMATION

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

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