ORIGINAL ARTICLE

Tolerability of nausea and vomiting and associations with weight loss in a randomized trial of liraglutide in obese, non-diabetic adults

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BACKGROUND: Liraglutide 3.0 mg, with diet and exercise, produced substantial weight loss over 1 year that was sustained over 2 years in obese non-diabetic adults. Nausea was the most frequent side effect.

OBJECTIVE: To evaluate routinely collected data on nausea and vomiting among individuals on liraglutide and their influence on tolerability and body weight.

DESIGN: A randomized, placebo-controlled, double-blind 20-week study with an 84-week extension (sponsor unblinded at 20 weeks, open-label after 1 year) in eight European countries (Clinicaltrials.gov: NCT00422058).

SUBJECTS: After commencing a 500-kcal/day deficit diet plus exercise, 564 participants (18–65 years, body mass index (BMI) 30–40 kg m\(^{-2}\)) were randomly assigned (after a 2-week run-in period) to once-daily subcutaneous liraglutide (1.2, 1.8, 2.4 or 3.0 mg), placebo or open-label orlistat (120 mg × 3 per day). After 1 year, participants on liraglutide/placebo switched to liraglutide 2.4 mg, and subsequently, to liraglutide 3.0 mg (based on 20-week and 1-year results, respectively).

RESULTS: The intention-to-treat population comprised 561 participants (n = 90–98 per arm, age 45.9 ± 10.3 years, BMI 34.8 ± 2.7 kg m\(^{-2}\) (mean ± s.d.)). In year 1, more participants reported ≥1 episode of nausea/vomiting on treatment with liraglutide 1.2–3.0 mg (17–38%) than with placebo or orlistat (both 4%, P < 0.001). Most episodes occurred during dose escalation (weeks 1–6), with ‘mild’ or ‘moderate’ symptoms. Among participants on liraglutide 3.0 mg, 48% reported some nausea and 13% some vomiting, with considerable variation between countries, but only 4 out of 93 (4%) reported withdrawals. The mean 1-year weight loss on treatment with liraglutide 3.0 mg from randomization was 9.2 kg for participants reporting nausea/vomiting episodes, versus 6.3 kg for those with none (a treatment difference of 2.9 kg (95% confidence interval 0.5–5.3); P = 0.02). Both weight losses were significantly greater than the respective weight losses for participants on placebo (P < 0.001) or orlistat (P < 0.05). Quality-of-life scores at 20 weeks improved similarly with or without nausea/vomiting on treatment with liraglutide 3.0 mg.

CONCLUSION: Transient nausea and vomiting on treatment with liraglutide 3.0 mg was associated with greater weight loss, although symptoms appeared tolerable and did not attenuate quality-of-life improvements. Improved data collection methods on nausea are warranted.

Keywords: GLP-1 analog; liraglutide; nausea; quality of life; vomiting; weight loss

INTRODUCTION

Obesity is described by the WHO (World Health Organization) as one of the most important public health threats. It is a major factor in the development of type 2 diabetes mellitus, cardiovascular disease, hypertension, certain cancers, sleep apnea, osteoarthritis and depression. Obese individuals often have lower self-esteem and a poorer quality of life (QoL) than do normal-weight individuals. Within routine primary care, diet and exercise-based intervention can be cost-effective, but only a small minority achieve the >5% weight loss at 12 and 24 months that is associated with improvements in obesity-related cardiovascular and metabolic risk factors. A largely unmet medical need for adjunctive and effective anti-obesity pharmacotherapy exists. The safety and side-effect profiles of pharmaceutical agents are in particular focus because obesity is usually a chronic condition demanding long-term treatment. Liraglutide is an analog of the incretin and satiety hormone, glucagon-like peptide-1 (GLP-1), which decreases energy intake and promotes weight loss and glucose-stimulated insulin release. Subcutaneous liraglutide (Victoza, Novo Nordisk A/S, Bagsvaerd, Denmark), at once-daily doses of up to 1.8 mg per day, is approved in the EU and US for the treatment of type 2 diabetes mellitus and liraglutide 3.0 mg per day is currently under investigation for weight management. A phase 2 randomized,
placebo-controlled trial in 564 obese non-diabetic adults showed that liraglutide was more effective than orlistat or diet and exercise alone at reducing weight (the primary endpoint).\textsuperscript{25,26}

From randomization, participants on liraglutide 3.0 mg lost 7.2 kg of mean body weight at 20 weeks and 7.8 kg at 1 year (analysis of covariance). After 2 years, participants who had been randomized to liraglutide 2.4 or 3.0 mg (pooled group) sustained a mean weight loss of 5.3 kg. Those completing the full 2-year treatment period lost 7.8 kg from the time of commencing weight loss at run-in. The most frequently reported side effect with liraglutide was nausea, known to be induced by supraphysiologically levels of native GLP-1 and by GLP-1 receptor agonists.\textsuperscript{14,18,27,28} In phase 3 trials of liraglutide for type 2 diabetes mellitus, nausea was reported by up to 40% of individuals on liraglutide 1.2 or 1.8 mg per day, but was mostly mild and transient.\textsuperscript{29} Similarly, in this trial involving obese individuals, nausea was also the most frequently reported side effect, occurring mostly early in the trial during dose escalation.\textsuperscript{25} Vomiting, reported less frequently, also had a higher incidence among individuals on liraglutide treatment.

The aim of the current paper was to document more closely the data on nausea and vomiting from the phase 2 trial of liraglutide at doses of up to 3.0 mg per day in non-diabetic obese adults,\textsuperscript{25,26} in terms of incidence and tolerability and the relationship to weight loss.

**PARTICIPANTS AND METHODS**

Full details of the study design and participants recruited have been published.\textsuperscript{25,26} Local ethics committees approved the trial protocol, and the trial was performed according to the Declaration of Helsinki\textsuperscript{25} and guidelines for Good Clinical Practice. The trial is registered with Clinicaltrials.gov, number NCT00422058.

Participants

Obese men and women gave informed written consent to participate in the trial, which was conducted at 19 clinical research centers in eight countries across Europe from January 2007 to April 2009. Eligible participants were aged 18–65 years and were of stable weight, with body mass index (BMI) of 30–40 kg m\(^{-2}\) and fasting plasma glucose of <7.0 mmol L\(^{-1}\) (126 mg dl\(^{-1}\)) at the start of the run-in period. Individuals were excluded if they had been diagnosed with type 1 or 2 diabetes mellitus or major medical conditions, had used approved weight-loss drugs within the previous 3 months, had received drug treatment known to induce weight gain or had received surgical obesity treatment.

Study design

The study design is shown in Figure 1. Participants commenced weight loss with a 2-week ‘run-in’ period (diet, exercise and placebo injections), starting one week after screening. They were then randomized to treatment for 20 weeks, and most consented to enroll in the extension, continuing blinded on randomized treatment for a further 32 weeks (52 weeks in total). At week 20, the sponsor was unblinded to liraglutide/placebo treatment, whereas the participants and investigators remained blinded up to 1 year. After 1 year, when the 20-week data had been analyzed, the trial was fully unblinded. At 1 year, participants on liraglutide and placebo treatment switched to open-label treatment with liraglutide 2.4 mg, deemed the optimal dose from analysis of the 20-week data, undergoing dose escalation as necessary. However, after analysis of the 1-year efficacy and safety data, the 3.0-mg dose was, instead, considered optimal. Participants on liraglutide 2.4 mg therefore switched to liraglutide 3.0 mg in weeks 70–96 (timing was variable, occurring as sites obtained ethics-committee approval). Individuals on orlistat remained on a standard 3 × 120-mg dose for the full 2-year period. For the current paper, weight changes from randomization are given. It is of note that there was an additional mean weight loss of 1.3 ± 1.4 kg during the run-in period prior to randomization.\textsuperscript{25}

Treatment

After the run-in period, individuals were randomly assigned to double-blind treatment (liraglutide, placebo or orlistat). Liraglutide doses of 1.2, 1.8, 2.4 or 3.0 mg were administered once daily by evening subcutaneous injection using a pre-filled injection pen (FlexPen, Novo Nordisk A/S, Bagsvaerd, Denmark) with NovoFine Needles 8 mm × 30 G (Novo Nordisk A/S), starting with doses of 0.6 mg per day and increasing by weekly increments of 0.6 mg (dose escalation). The open-label comparator group was randomized to receive orlistat capsules (3 × 120 mg per day) (Xenical, Roche, Basel, Switzerland) with each main meal for the full 2-year period. During the run-in period and throughout treatment, all participants received dietary counseling for a nutritionally balanced low-calorie diet (with about 30% of total caloric intake from fat, 20% from protein and 50% from carbohydrates), providing an energy deficit of approximately 500 kcal per day below the estimated 24-h energy requirements\textsuperscript{31} (calculated as basal metabolic rate × physical activity level 1.3). Participants were also advised to maintain or increase physical activity.

Study measures

For regulatory purposes, side effects were recorded as adverse events and as responses to open questions at every visit or telephone contact from screening and up to 1 week after the last day on treatment. All adverse events (serious and non-serious) were coded using the Medical Dictionary for Regulatory Activities version 10.1. Information about nausea or vomiting was thus collected as part of a routine adverse event collection.

Figure 1. Study design. *During 20–52 weeks, participants/investigators remained blinded to liraglutide/placebo treatment, but the sponsor was unblinded; after 1 year, all were unblinded.
Participants had been made aware in the baseline subject information/ informed consent material of the main side effects of liraglutide (‘diarrhea, nausea and in rare cases vomiting, and also headache and dizziness’). All events observed by the investigator or reported by participants either spontaneously or in response to open questions were recorded by the investigator on an adverse event form; these data were used as the basis for measuring the incidence of nausea and vomiting. The following information was recorded on the form: adverse-event diagnosis (if known, otherwise symptoms were listed), whether the event was serious or of special interest (requiring completion of a separate form), the date of onset, severity (mild, moderate or severe), outcome (recovered, recovering, recovered with sequelae, not recovered, fatal or unknown), causality in relation to the trial product (in the investigator’s opinion) and whether any action regarding trial products was taken. A ‘mild’ event was characterized by ‘no or transient symptoms, no interference with the subject’s daily activities’; a ‘moderate’ event was characterized by ‘marked symptoms, moderate interference with the subject’s daily activities’; and a ‘severe’ event was characterized by ‘considerable interference with the subject’s daily activities unacceptable’.

According to the protocol, trial drug dose reduction or increase was not allowed, and participants were to be withdrawn if they could not tolerate treatment. However, intermittent pauses and slower dose escalation were permitted on a case-by-case basis, after discussion with the sponsor.

A ‘serious’ adverse event was one that resulted in at least one of the following outcomes: death, life-threatening experience, in-patient hospitalization or prolongation of existing hospitalization, persistent or significant disability, a congenital anomaly/birth defect or any event that, based on appropriate medical judgment, jeopardizes the individual and may require medical or surgical intervention to prevent one of the described outcomes.

Health-related QoL was assessed using the Impact of Weight on Quality of Life—Lite (IWQoL-Lite) questionnaire. The IWQoL-Lite is a validated, 31-item, self-reported measure of weight-related QoL that assesses physical function, self-esteem, sexual life, public distress and work. Finally, body weight was measured at every visit, starting from the screening visit, using calibrated scales.

Statistical analysis

The sample size estimation for the 20-week trial has been reported previously. The effect of at least one episode of nausea/vomiting on weight change was investigated by analysis of covariance, and the effect of gender on the reporting of episodes of nausea/vomiting, as well as the incidence of these, was tested using logistic regression. These were post-hoc analyses performed on a modified intention-to-treat population (comprising randomized individuals having at least one treatment dose and at least one post-randomization assessment) using last-observation-carried-forward. Analyses at year 1 tested the superiority of each liraglutide dose over placebo and orlistat. At year 2, the superiority of liraglutide 3.0 mg, 82 (88%) completed 20 weeks and 65 remained on liraglutide 3.0 mg at 1 year (30% withdrawals, including 10 who elected not to enroll in the extension at 20 weeks). At 2 years, 47 of the participants randomized to liraglutide 3.0 mg were still taking this dose (2-year withdrawal rate = 49%).

Three individuals randomized to liraglutide were excluded from the intention-to-treat population owing to missing post-randomization weight data. Major protocol deviations during the trial have been described previously.

Participant characteristics were comparable across groups at randomization (Table 1) and on entering the extension (not shown). The mean age was 45.9 ± 10.3 (s.d.) years, and BMI was 34.8 ± 2.7 kg m⁻².

Incidence of nausea and vomiting during year 1

The frequency of nausea and/or vomiting for women (n = 135; 19% (95% confidence interval (CI) 13–26%)) was not statistically significantly different from that of men (n = 29; 12% (95% CI 7–20%)); the odds ratio (female: male) was 1.7 (95% CI: 0.9–3.1; P = 0.09). The proportion of individuals reporting nausea/vomiting at any time during year 1 on liraglutide was dose-dependent (Figure 2a), and statistically significantly greater than with placebo and orlistat for all liraglutide doses.

Reporting of nausea and vomiting by country

Reported incidence of nausea and vomiting varied widely between the eight recruiting countries (Figures 2b and c). The proportion of individuals on liraglutide (all doses) who reported nausea ranged from 0/47 (%) (Czech Republic) to 27/75 (36%) (UK), and the proportion on liraglutide who reported vomiting ranged from 0/11 (%) (Belgium) to 13/75 (17%) (UK).

Timing

Most episodes of nausea (42/68 (62%)) among individuals on liraglutide 3.0 mg were first reported in weeks 1–4, during dose escalation (Table 2). A total of 7 out of 16 (44%) vomiting bouts were reported in weeks 1–4, and 11 out of 16 (67%) were reported in weeks 1–6 among individuals on liraglutide 3.0 mg. No correction for multiplicity adjustment. All analyses were two-sided, with 5% significance, and were performed using the Statistical Analysis System software package (version 9.1; SAS Institute, Cary, NC, USA).

Results

Trial population

Of 616 individuals entering the 2-week run-in period, 52 (8%) withdrew, leaving 564 to receive randomized treatment: 135 men (24%) and 429 women (76%). 472 completed the 20-week trial and 398 chose to enroll in the extension period (74 discontinued), with 268 completing the full 2-year period (Figure 1 and Supplementary Figure 1). Of the 93 participants randomized to liraglutide 3.0 mg, 82 (88%) completed 20 weeks and 65 remained on liraglutide 3.0 mg at 1 year (30% withdrawals, including 10 who elected not to enroll in the extension at 20 weeks). At 2 years, 47 of the participants randomized to liraglutide 3.0 mg were still taking this dose (2-year withdrawal rate = 49%).

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participant in any group reported \( \geq 4 \) nausea episodes. Episodes of nausea reported by individuals on liraglutide 3.0 mg after week 8 were mainly reported by those who had already experienced earlier episodes (15/18 (83%). Most nausea and vomiting episodes were transient (data not shown). Data collected for regulatory purposes did not allow an exact assessment of the duration of reported symptoms or the frequencies of transient symptoms occurring between visits and assessments.

Withdrawals and temporary dose reduction
Most liraglutide 3.0 mg recipients who experienced nausea (36/45 participants (80%)) or vomiting (9/12 (75%)) reported only one episode, and only 4 out of 93 (4%) withdrew because of nausea/vomiting (one withdrew because of nausea; one withdrew because of vomiting; one withdrew because of nausea and vomiting; and one withdrew because of vomiting and diarrhea). In addition to withdrawals owing to nausea and vomiting (Table 2), one participant on liraglutide 1.8 mg and 2 on 2.4 mg withdrew for ‘other’ reasons (specifically, intolerance to the allocated dose) after 102, 64 and 65 days, respectively. No nausea episodes in the first year were rated ‘serious’ or led to temporary dose reduction or drug withdrawal.

Severity
Most reported episodes of nausea and vomiting were of ‘mild’ or ‘moderate’ intensity (Figure 2d). Among individuals on liraglutide,

Figure 2. (a) The proportion of individuals reporting nausea/vomiting at any time during year 1 (logistic regression analysis). Data are estimated means. Odds ratios (OR) versus placebo/orlistat are shown, together with 95% CI. The proportion of participants reporting nausea (b) and vomiting (c) by country in year 1. (d) Severity of nausea and vomiting episodes reported in year 1. (e) The proportion of individuals with nausea at any time during 2 years of treatment, by week. Safety analysis set.

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Table 2. Incidence of nausea and vomiting during the 2-year trial period

| Treatment: | Placebo | 1.2mg | 1.8mg | 2.4mg | 3.0mg | Orlistat |
|------------|---------|-------|-------|-------|-------|---------|
| Year 1     |         |       |       |       |       |         |
| Nausea     | n = 98  |       |       |       |       |         |
| N (%) episodes starting in weeks 1–4 | 7 (7.1%) | 23 (24%) | 27 | 29 (32%) | 33 | 35 (38%) | 48 | 45 (48%) | 68 | 7 (7.4%) | 7 |
| Vomiting   | n = 95  |       |       |       |       |         |
| N (%) episodes starting in weeks 1–4 | 5 (5.3%) | 21 (22%) | 17 | 23 (26%) | 26 | 29 (32%) | 32 | 35 (35%) | 40 | 5 (5.3%) | 5 |
| N (%) individuals with only 1 episode | 4/2 (100%) | 6 (6%) | 6 | 9 (10%) | 18 | 14 (15%) | 17 | 12 (13%) | 16 | 2 (2.1%) | 4 |
| Year 2     |         |       |       |       |       |         |
| Nausea     | n = 67  |       |       |       |       |         |
| N (%) episodes starting in weeks 1–4 | 32 (48%) | 18 (26%) | 20 | 7 (12%) | 7 | 10 (15%) | 13 | 6 (8.3%) | 7 | 1 (1.5%) | 1 |
| Vomiting   | n = 68  |       |       |       |       |         |
| N (%) episodes starting in weeks 1–4 | 5 (7.5%) | 8 (12%) | 9 | 5 (8.5%) | 6 | 2 (3.1%) | 3 | 1 (1.4%) | 1 | 1 (1.5%) | 2 |

Serious episodes

| Nausea     |       |       |       |       |       |         |
| Vomiting   |       |       |       |       |       |         |

Episodes leading to withdrawal

| Nausea     |       |       |       |       |       |         |
| Vomiting   |       |       |       |       |       |         |

Treatment:

| Liraglutide 2.4mg then 3.0mg | Orlistat |
|-------------------------------|----------|
| Year 2                        |          |
| Nausea                        | n = 67   | n = 68 | n = 59 | n = 65 | n = 72 | n = 67 |
| Vomiting                      |          |        |        |        |        |        |

Serious episodes

| Nausea     |       |       |       |       |       |         |
| Vomiting   |       |       |       |       |       |         |

Episodes leading to withdrawal

| Nausea     |       |       |       |       |       |         |
| Vomiting   |       |       |       |       |       |         |

Abbreviations: E, number of adverse events; N (%), number and proportion of participants with an adverse event. *All on liraglutide/placebo switched to liraglutide 2.4 mg at week 52, then between 70–96 weeks to 3.0 mg.
73% of reported episodes of nausea were ‘mild’, 25% were ‘moderate’, and only 2% were ‘severe’. For vomiting, 46% of episodes were ‘mild’, 46% ‘moderate’, and 9% ‘severe’. Sixteen episodes of nausea among individuals on liraglutide were noted as ‘intermittent nausea’ by the participant/investigator, compared with two in the placebo group and one in the orlistat group; and six cases of ‘intermittent vomiting’ were reported among individuals on liraglutide.

Two episodes of vomiting were rated as ‘serious’ (Table 2). One serious episode started after 135 days on liraglutide 2.4 mg, and recovery was registered after 2 days, occurring at the same time as events of epigastric abdominal pain, nausea, headache and loss of vision in the left eye. This woman recovered from the events with no dose reduction, but withdrew consent to continue in the trial in year 2. She had other gastrointestinal disturbances during the trial (including diarrhea, retching and constipation as well as the above). The other serious vomiting episode had its onset after 266 days of treatment with liraglutide 3.0 mg, occurring simultaneously with an event of abdominal pain. Liraglutide was temporarily withdrawn; the woman recovered after 8 days and eventually completed the trial. She also had other gastrointestinal disorders (including nausea and constipation) as well as cholelithiasis (gallstones). Weight loss data for the two individuals who experienced the above events were not available.

Three non-serious vomiting episodes led to temporary dose reduction or drug withdrawal. Liraglutide dose was reduced after 22 days (during escalation to 2.4 mg) for one individual, who subsequently withdrew because of nausea on day 33. Another individual in the liraglutide 2.4 mg group had a temporary dose reduction after 2 days on account of vomiting, but recovered after 1 day and completed the trial. One in the orlistat group had treatment temporarily withdrawn because of vomiting after 123 days (but recovered after 3 days and completed the trial).

Incidence of nausea and vomiting during year 2

The proportion of individuals experiencing nausea at any time during 2 years of treatment is shown in Figure 2e. Just as the incidence of nausea was highest during dose escalation at the start of the trial, nausea was again observed at the start of the second year in individuals in the placebo and liraglutide 1.2 and 1.8 mg groups, when they switched to liraglutide 2.4 mg. During the 4-week dose-escalation period starting year 2, 23 individuals (34%) who were previously on placebo experienced some nausea, which was similar to the proportion undergoing dose escalation to 2.4 mg in the first year (32%). Only 3 of those 23 participants had experienced nausea in year 1 while on placebo. Fewer individuals who were already on liraglutide 1.2 and 1.8 mg reported nausea during dose escalation to 2.4 mg: 16 and 6.8%, respectively. Only one individual in each group already treated with liraglutide 2.4 and 3.0 mg experienced nausea in the first 4 weeks of year 2. No participant experienced vomiting in the group randomized to placebo during dose escalation to 2.4 mg, whereas 11 (12%) randomized to 2.4 mg had reported vomiting in the first 4 weeks of the trial.

Association between nausea/vomiting and weight loss

After 1 year of treatment, the estimated mean weight loss from randomization with liraglutide 3.0 mg was 9.2 kg for those who experienced at least one episode of nausea/vomiting (n = 49) and 6.3 kg for those who did not (n = 43) (a treatment difference of 2.9 kg (95% CI 0.5–5.3); P = 0.02) (Figure 3a). With liraglutide 3.0 mg, weight loss in individuals who reported no nausea/vomiting was still significantly greater than in those on both placebo (a treatment difference of 4.2 kg (2.1–6.4); P = 0.0001) and orlistat (a treatment difference of 2.3 kg (0.14–4.4); P = 0.04). The mean 1-year weight loss in individuals on liraglutide 3.0 mg who did experience episodes of nausea/vomiting was 7.8 kg (3.4–12.2) greater than in those on placebo (P = 0.0006) and 6.6 kg (2.1–11.0) greater than in those on orlistat (P = 0.004).

The estimated mean weight loss from randomization to year 2 for participants on liraglutide 2.4/3.0 mg (pooled group) was also significantly greater for those who experienced at least one episode of nausea/vomiting (6.9 kg, n = 93) compared with those who did not (4.1 kg, n = 91) (a treatment difference of 2.9 kg (0.8–4.9); P = 0.006) (Figure 3b).

Association between nausea/vomiting and QoL

QoL scores at 20 weeks improved from randomization among individuals on liraglutide 3.0 mg, and mean scores for physical function, self-esteem and work were significantly greater than for those on placebo, as previously reported. No statistically significant differences were observed between individuals on liraglutide 3.0 mg who reported at least one episode of nausea/vomiting over 20 weeks and those who did not (Figure 4).

DISCUSSION

We investigated the effects of liraglutide (at doses of up to 3.0 mg per day) on the incidence and tolerability of nausea and vomiting, as well as on weight loss, in obese non-diabetic individuals. Although these events were reported more often with liraglutide than with either placebo or orlistat, symptoms were mostly mild or moderate, transient and remarkably well tolerated. Nausea and vomiting were associated with up to 2.9 kg more weight loss after 1 year of treatment, which suggests an association with at least part of the mechanism of action of liraglutide-induced weight loss. However, QoL assessed at 20 weeks was not impaired, even at the highest 3.0-mg dose, which induced nausea in almost 50% of individuals, mainly in weeks 1–4 during dose escalation. The incidence of vomiting was lower, about a quarter of that of...
the 13 countries involved. Notably in the current trial, nobody in the reporting rates of general and serious adverse events across clinical trials of gastrointestinal indications, there were differences in the study of geographical variation in adverse-event reporting in 127 countries. Variability in the assessment of adverse events in clinical trials has been previously reported. Considerable differences in the way investigators inquired about and reported adverse events. The nature of this process, as well as possible differences in the way investigators inquired about and reported adverse events in the different centers and countries, may have affected the recording of these events. For instance, the incidence of reported nausea and vomiting in the eight recruiting countries varied substantially. The lack of systematic data collection on nausea and vomiting, and duration of episodes, is a limitation of this study, but is also an important lesson for future clinical trials.

These data originate from a clinical trial whose primary aim was to investigate weight changes. Although information about nausea and vomiting was not collected using a specific questionnaire, it was possible to gain a reasonably clear understanding about such events from the data routinely reported on adverse events. The nature of this process, as well as possible differences in the way investigators inquired about and reported adverse events in the different centers and countries, may have affected the recording of these events. For instance, the incidence of reported nausea and vomiting in the eight recruiting countries varied substantially. The lack of systematic data collection on nausea and vomiting, and duration of episodes, is a limitation of this study, but is also an important lesson for future clinical trials.

Figure 4. Mean (analysis of covariance) changes (positive = improved) in quality-of-life scores (IWQoL-Lite) among individuals on liraglutide 3.0 mg at 20 weeks, in individuals with or without at least one episode of nausea or vomiting (intention-to-treat population with the last observation carried forward). IWQoL-Lite scores ranged from 0 (worst) to 100 (best).

Confl ict of interest

Liraglutide is a Novo Nordisk A/S proprietary compound under development for the treatment of obesity. No payments were made to the authors for the present paper.
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APPENDIX

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