Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial

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Summary

Background

Agonists of the glucagon -like peptide-1 (GLP-1) receptor provide pharmacological levels of GLP-1 activity, whereas dipeptidyl peptidase-4 (DPP-4) inhibitors increase concentrations of endogenous GLP-1 and glucose-dependent insulinotropic polypeptide. We aimed to assess the efficacy and safety of the human GLP-1 analogue liraglutide {Victoza} versus the DPP-4 inhibitor sitagliptin {Januvia}, as adjunct treatments to metformin, in individuals with type 2 diabetes who did not achieve adequate glycaemic control with metformin alone.

Methods

In this parallel-group, open-label trial, participants (aged 18-80 years) with type 2 diabetes mellitus who had inadequate glycaemic control (glycosylated haemoglobin [HbA1c] 7.5-10.0%) on metformin (≥1500 mg daily for ≥3 months) were enrolled and treated at office-based sites in Europe, the USA, and Canada. Participants were randomly allocated to receive 26 weeks' treatment with 1.2 mg (n=225) or 1.8 mg (n=221) subcutaneous liraglutide once daily, or 100 mg oral sitagliptin once daily (n=219). The primary endpoint was change in HbA1c from baseline to week 26. The efficacy of liraglutide versus sitagliptin was assessed hierarchically by a non-inferiority comparison, with a margin of 0.4%, followed by a superiority comparison. Analyses were done on the full analysis set with missing values imputed by last observation carried forward; seven patients assigned to liraglutide did not receive treatment and thus did not meet criteria for inclusion in the full analysis set. This trial is registered with ClinicalTrials. gov, number NCT00700817.

Findings

Greater lowering of mean HbA1c (8.5% at baseline) was achieved with 1.8 mg liraglutide (-1.50%, 95% CI -1.63 to -1.37, n=218) and 1.2 mg liraglutide (-1.24%, -1.37 to -1.11, n=221) than with sitagliptin (-0.90%, -1.03 to -0.77, n=219). Estimated mean treatment differences for liraglutide versus sitagliptin were -0.60% (95% CI -0.77 to -0.43, p<0.0001) for 1.8 mg and -0.34% (-0.51 to -0.16, p<0.0001) for 1.2 mg liraglutide. Nausea was more common with liraglutide (59 [27%] patients on 1.8 mg; 46 [21%] on 1.2 mg) than with sitagliptin (10 [5%]). Minor hypoglycaemia was recorded in about 5% of participants in each treatment group.

Interpretation

Liraglutide was superior to sitagliptin for reduction of HbA1c, and was well tolerated with minimum risk of hypo glycaemia. These findings support the use of liraglutide as an effective GLP-1 agent to add to metformin.

Funding

Novo Nordisk.

Introduction

The health-care burden of diabetes, especially type 2 diabetes mellitus, continues to increase. An estimated 285 million people worldwide have diabetes at present, and 439 million are expected to have diabetes by 2030.[1] Vascular complications are responsible for most of the associated morbidity, mortality, and excess costs.[2] Although good glycaemic control can decrease the risk of microvascular, and possibly macrovascular complications, [3] many people with type 2 diabetes are not achieving glycaemic goals,[4] partly because of the low efficacy and adverse side-effects of available drugs. New treatments with improved efficacy and fewer side-effects are needed.

Therapies targeting the incretin system are important for management of type 2 diabetes. Two principal incretin hormones —glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)—are rapidly released after meals. [5] Both hormones augment glucose-dependent insulin secretion; and GLP-1, but not GIP, also suppresses glucagon secretion, delays gastric emptying, and decreases food intake.[5] GLP-1 and GIP are inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4). [5] Incretin-based therapies consist of two drug classes: GLP-1 receptor agonists, which have biological activity similar to GLP-1, but are resistant to DPP-4; and DPP-4 inhibitors, which prevent enzymatic inactivation of endogenous GLP-1 and GIP.[6] Both classes increase insulin secretion and decrease glucagon secretion in a glucose-dependent manner, but with differences. GLP-1 receptor agonists (eg, exenatide, and the human GLP-1 analogue liraglutide) need injection. Glycaemic benefits of native GLP-1 or a GLP-1 receptor agonist (dosed to pharmacological concentrations) are accompanied by delayed gastric emptying and weight loss, but nausea initially occurs in some people.[5-7] By contrast, oral DPP-4 inhibitors (eg, sitagliptin, vildagliptin, saxagliptin) increase active endogenous GLP-l and GLP to more modest physiological concentrations.[5-7] DPP-4 inhibitors do not delay gastric emptying, promote weight loss, or typically cause nausea, presumably because of lower GLP-l concentrations.[5-7]

In clinical trials, agonists of the GLP-1 receptor and DPP-4inhibitors improve glycaemic control when given as

monotherapy or added to metformin, sulphonylureas, or thiazolidinediones; the intrinsic risk of hypo glycaemia is low but increases with sulphonylureas.[8-18] Few direct comparisons of incretin-based therapies have been published, including long-term prospective comparison of a GLP-l analogue and DPP-4 inhibitor. We aimed to compare the efficacy and safety of treatment with liraglutide or sitagliptin for 26 weeks in individuals with type 2 diabetes who did not achieve adequate glycaemic control with metformin.

Methods

Participants

The study was done in 158 office-based sites in 11 European countries (Croatia, Germany, Ireland, Italy, Netherlands, Romania, Serbia, Slovakia, Slovenia, Spain, and UK), the USA, and Canada between June 16, 2008, and June 11, 2009. Participants were eligible if they were aged 18-80 years, had type 2 diabetes mellitus, had glycosylated haemoglobin (HbAlc) of 7.5-10.0%, had a body-mass index of 45.0 kg/m^2 or lower, and had been treated with metformin (≥1500 mg daily) for 3 months or longer. Main exclusion criteria were: previous treatment with any antihyperglycaemic drug apart from metformin within 3 months of the trial; recurrent major hypoglycaemia or hypoglycaemic unawareness; present use of any drug except metformin that could affect glucose; contraindication to trial drugs; impaired renal or hepatic function; clinically significant cardiovascular disease; or cancer (for detailed exclusion criteria see webappendix pp 1-2).

We adhered to Good Clinical Practice guidelines issued by the International Conference on Harmonisation, and to the Declaration of Helsinki. Independent local ethics committees approved the protocol, amendments, and informed consent documents. Participants provided written consent before study procedures began.

Randomisation and masking

The randomisation sequence was computer-generated by Novo Nordisk. Participants were randomly assigned in a 1:1:1 ratio, stratified by country, to receive 1.2 mg or 1.8 mg subcutaneous liraglutide once daily, or 100 mg oral sitagliptin once daily. Consecutive allocation of the randomisation code to individual participants was concealed by use of a telephone-based (interactive voice response system) or web-based (interactive web response system) randomisation system. Details of random allocation and implementation were similar to those described for the LEAD-6 study[9] (for randomisation details see web appendix p 2). The study was open-label, but data were masked from the statistician until database release.

Procedures

In this active-comparator, parallel-group trial, participants received treatment for 26 weeks. Liraglutide (Novo Nordisk, Bagsvaerd, Denmark) was started at 0.6 mg/day and escalated by 0.6 mg/week to the allocated dose; injection was done subcutaneously with a pen device. Sitagliptin (Merck, Whitehouse Station, NJ, USA) was started and maintained at 100 mg/day, Participants were encouraged to take medication at the same time every day. After randomisation, trial and background treatment with metformin remained stable; participants who did not tolerate trial treatment doses were withdrawn. Participants were judged to have received treatment if they had taken at least one dose of study drug. After the 26-week study, participants could continue into a 12-month follow-up phase that is underway.

The primary efficacy endpoint was change in HbA1c from baseline to week 26. Secondary endpoints recorded at baseline and week 26 were: proportions of participants reaching HbA1c targets of less than 7.0% (as recommended by the American Diabetes Association) or of 6.5% or lower (American Association of Clinical Endocrinologists, International Diabetes Federation, and National Institute of Clinical Health and Excellence); fasting plasma glucose; postprandial plasma glucose; bodyweight; β-cell function; fasting lipid profile; cardiovascular risk markers (high-sensitivity C-reactive protein, plasminogen activator inhibitor type 1, N-terminal pro-B-type natriuretic peptide, adiponectin, interleukin 6, tumour necrosis factor a, and von Willebrand factor); blood pressure; heart rate; physical measures (waist circumference, waist-to-hip ratio); treatment satisfaction; and a composite endpoint of proportions of participants with HbA1c of less than 7.0%, with no hypoglycaemia, and weight change of 0 kg or less. Treatment satisfaction was assessed with the eight-item Diabetes Treatment Satisfaction Questionnaire (DTSQ)[19] in a subgroup of 505 participants; overall treatment satisfaction was the sum of six of the eight DTSQ items.

Safety assessments included adverse events, self. reported hypo glycaemia, and selected haematological and biochemical measures, including calcitonin. Minor hypoglycaemic episodes (plasma glucose <3.1 mmol/L] were self-treated; for major episodes, third-party assistance was needed, irrespective of glucose concentrations, and these episodes were recorded as adverse events. HbA1c was measured by high-performance liquid chromatography certified by the National Glycohaemoglobin Standardization Program. Central laboratories (MDS Pharma Services) in Baillet, France, and North Brunswick, NJ, USA, did assays. Participants used MediSense Precision glucose meters (Abbott Diagnostics, Abbott Park, IL, USA; coefficient of variation ≤5.2%) to measure glucose values for patient diaries.

Statistical analyses

The effectiveness of liraglutide (versus sitagliptin) was assessed hierarchically by a non-inferiority comparison, with a margin of 0.4%, and then by a superiority comparison. On the basis of the primary endpoint and the non-inferiority margin, we calculated that 163 participants per group were needed for 85% power, and with a predicted withdrawal of 25%, 217 participants per group were needed. Non-inferiority and superiority were tested as two-sided hypotheses, with p values of less than 0.05 judged to be significant. Primary efficacy analyses were done on the full analysis set (randomised participants who were exposed to at least one dose of trial drug and with at least one HbA1c measurement taken after baseline) with missing values imputed by last observation carried forward, and on the per-protocol set. For non-inferiority, we expected similar outcomes to be recorded with the full analysis and per-protocol sets, but for superiority, we judged the full analysis set to be primary. We present data for the full analysis set.

Secondary efficacy analyses were done on the full analysis set, apart from treatment satisfaction analyses, in which missing data were not imputed because data were only available for screening and randomisation (baseline) visits. Most endpoints were assessed by ANCOVA, with treatment and country as fixed effects, and baseline measure as a covariate. We used logistic regression to compare the proportions of participants achieving HbA1c targets and the composite endpoint, and generate odds ratios (ORs). Treatment was a fixed effect, and baseline HbA1c was a covariate, with baseline weight as an additional covariate for

the composite endpoint only. Safety analyses were done on data from all patients who had been exposed to at least one dose of trial drug. Hypoglycaemic episodes were analysed by a general linear model with treatment as a fixed effect. Calcitonin concentrations were analysed with a repeated measures model with sex, time, treatment, and treatment-by-time interaction as fixed effects, and participant as a random effect. Other safety data were compared by descriptive statistics. Data are expressed as least squares mean with 95% CI unless stated otherwise. Statistical analyses were done with SAS software (version 9.13) on a UNIX platform.

Further procedural and statistical information is provided in webappendix pp 2-4. This trial is registered with ClinicalTrials.gov, number NCT00700817.

Role of the funding source

The study sponsor participated in the study design, data collection, data review, and data analysis. The corresponding author reviewed the trial report (signatory investigator), had full access to all data in the study, and had final responsibility for the decision to submit for publication. All other authors were investigators who had full access to data.

Results

Of 1302 patients assessed, 665 participants were randomly assigned to treatment. 658 (99%) received at least one dose of trial drug, and 554 (83%) completed the trial (figure 1). Demographic characteristics were well balanced across treatment groups; overall, mean HbA1c was 8.5% (SD 0.7) at baseline (table 1). Numbers of withdrawals were similar for patients on 1.8 mg liraglutide and sitagliptin, but higher for those on 1.2 mg liraglutide (figure 1).

In the superiority comparison, HbA1c reductions were superior with 1.2 mg and 1.8 mg liraglutide versus sitagliptin (figure 2A and 2B). After 26 weeks, mean decreases in HbA1c from baseline were -1.50% (95% CI -1.63 to -1.37) for 1.8 mg liraglutide, -1.24% (-1.37 to -1.11) for 1.2 mg liraglutide, and -0.90% (-1.03 to -0.77) for sitagliptin (figure 2B). Estimated mean treatment differences were -0.60% (95% CI -0.77 to -0.43) for 1.8 mg liraglutide versus sitagliptin, and -0.34% (-0.51 to -0.16) for 1.2 mg liraglutide versus sitagliptin (figure 2B). Treatment differences for the analysis with the per-protocol set and full analysis set without imputation were similar to those derived for the full analysis set with imputation. For the full analysis set with imputation in participants with baseline HbA1c of 9.0% or higher (n=154 participants), HbA1c decreased by -1.9% for those on 1.8 mg liraglutide, -2.2% for those on 1.2 mg liraglutide, and -1.4% for those on sitagliptin. Supplemental results for the primary endpoint of the per-protocol population, post-hoc testing of liraglutide (1.2 mg vs 1.8 mg), and ANCOVA for the primary endpoint are shown in webappendix pp 4-5.

Significantly more participants achieved the HbA1c targets (<7.0% and ≤6.5%) with liraglutide than with sitagliptin (figure 3A): for HbA1c of less than 7.0%, ORs versus sitagliptin were 4.50 (95% CI 2.90-6.97) for 1.8 mg liraglutide, and 2.75 (1.78-4.25) for 1.2 mg liraglutide; and for HbA1c of 6.5% or lower, ORs versus sitagliptin were 4.25 (2.55-7.08) for 1.8 mg liraglutide, and 2.11 (1.24-3.59) for 1.2 mg liraglutide. After 26 weeks, mean decreases in fasting plasma glucose were significantly greater with liraglutide than with sitagliptin (figure 3B): -2.14 mmol/L (95% CI -2.43 to -1.84) for 1.8 mg liraglutide; -1.87 mmol/L (-2 .16 to -1.57) for 1.2 mg liraglutide, and -0.83 mmol/L (-1.13 to -0.54) for sitagliptin. Estimated least squares mean treatment differences were -1.31 mmol/L (95% CI -1.70 to -0.91) for 1.8 mg liraglutide versus sitagliptin, and -1.04 mmol/L (-1.43 to -0.64) for 1.2 mg liraglutide versus sitagliptin. We do not report mean reductions in the area under the curve for postprandial plasma glucose because data were difficult to interpret. The time of day when postprandial plasma glucose was recorded was highly variable, suggesting that glucose values were not postprandial in many cases. Moreover, meal patterns (content and time of day) were very different across different countries.

Mean weight loss after 26 weeks was significantly greater with liraglutide than with sitagliptin (figure 3C): -3.38 kg (95% CI -3.91 to -2.84) for 1.8 mg liraglutide; -2.86 kg (-3.39 to -2.32) for 1.2 mg liraglutide, and -0.96 kg (-1.50 to -0.42) for sitagliptin. Estimated mean treatment differences were -2.42 kg (95% CI -3.14 to -1.70) for 1.8 mg liraglutide versus sitagliptin, and -1.90 kg (-2.61 to -1.18) for 1.2 mg liraglutide. Both liraglutide doses were associated with significantly greater reductions in waist circumference than sitagliptin, but no significant treatment-related differences of waist-to-hip ratio were noted (table 2). 46% (99/214) of participants on 1.8 mg liraglutide, 37% (77/210) of those on 1.2 mg liraglutide, and 14% (30/210) of those on sitagliptin achieved the composite secondary endpoint; measurements scheduled to be taken after baseline were missing for some participants, ORs versus sitagliptin were 5.46 (95% CI 3.37-8.85, p<0.0001) for 1.8 mg liraglutide, and 3.45 (2.12-5.61, p<0.000l) for 1.2 mg liraglutide.

In assessment of β-cell function, both liraglutide doses were associated with significant improvements in homoeostasis model assessment (HOMA) of β-cell function, C-peptide concentration, and proinsulin-to-insulin ratio compared with sitagliptin, but no treatment-related differences were recorded for HOMA index of insulin resistance, or fasting insulin concentration (table 2). Both liraglutide and sitagliptin had a small effect on systolic and diastolic blood pressure; lowering of diastolic blood pressure with sitagliptin seemed to be significant versus 1.8 mg liraglutide, but not versus 1.2 mg liraglutide (table 2). Heart rate increased with liraglutide, and decreased slightly with sitagliptin; differences were small but significant for both doses of liraglutide versus sitagliptin (table 2). Changes in the lipid profile between liraglutide and sitagliptin were not significant, apart from the decrease in total cholesterol which was significantly greater with 1.8 mg liraglutide than with sitagliptin (table 2).

Generally, improvements were seen in all DTSQ items for all treatment groups. The increase in patients' treatment satisfaction from baseline was significantly higher with 1.8 mg liraglutide than with sitagliptin (n=171 vs n=170; difference 1.39, 95% CI 0.13-2.64), but the increase with 1.2 mg liraglutide versus sitagliptin was not significant (figure 3D). Data for individual DTSQ items will be reported separately. No difference in perceived convenience of treatment (oral vs injection) was recorded between sitagliptin and liraglutide. Data for the noninferiority comparisons for the secondary endpoints are given in webappendix pp 4-7.

More treatment-emergent adverse events were reported with liraglutide than with sitagliptin (table 3). Serious adverse events occurred in 3% of participant or fewer, and severe adverse events occurred infrequently in all groups. Two deaths occurred, neither of which was judged as likely to be related to the study drug: one in a patient diagnosed with pancreatic carcinoma (day 11 of treatment with 1.8 mg liraglutide) who was withdrawn from the study and later died; and one in a patient who had a fatal cardiac arrest (day 48 of treatment with sitagliptin). The most common adverse events were gastrointestinal symptoms, especially with liraglutide, and infections and infestations, which occurred with similar frequency in all treatment groups. The distribution of most other adverse events was similar between treatment groups (table 3).

Nausea occurred in a higher proportion of patients on 1.8 mg and 1.2 mg liraglutide than on sitagliptin (table 3). Nausea with liraglutide was, however, transient (figure 4); in patients with nausea, the median duration was 13 days (IQR 5-28) with 1.2 mg liraglutide, 8 days (IQR 3-30) with 1.8 mg liraglutide, and 26 days (IQR 3-51) with sitagliptin. One patient on 1.2 mg liraglutide had a major hypoglycaemic episode (blood glucose concentration of 3.6 mmoljL); no seizures or coma occurred. Minor hypo glycaemia was reported by similar proportions of participants treated with 1.8 mg liraglutide (11 [5%], 0.370 episodes per participant-year), 1.2 mg liraglutide (12 [5%], 0 .178), and sitagliptin (10 [5%], 0 .106); with the exclusion of one outlier, occurrence was similar with 1.8 mg liraglutide (0 .161 episodes per participant-year) to that with the other treatment groups. One thyroid disorder (reported as a suspected formation in the thyroid gland) in a patient on 1.2 mg liraglutide was classified as a serious adverse event, but histology showed no signs of malignancy. Change from baseline in serum calcitonin concentrations, monitored for any effect on C-cell function, was similar across groups. No pancreatitis occurred in this study.

Further details and analyses of endpoints are shown in webappendix pp 4-7.

Discussion

We have shown that in people with inadequate glycaemic control on metformin, addition of daily doses of 1. 2 mg or 1. 8 mg liraglutide provides superior glycaemic control to addition of 100 mg sitagliptin daily, as assessed from reductions in HbA1c and fasting plasma glucose. In UKPDS,[3] a 1% reduction in HbA1c was associated with a 37% decreased risk of microvascular complications and a 21% decreased risk of death related to diabetes. These results suggest that the differences in HbA1c between liraglutide and sitagliptin that were recorded in our study are clinically relevant.[3] In accordance with the consensus algorithm for the treatment of type 2 diabetes mellitus by the American Diabetes Association and the European Association for the Study of Diabetes,[20] our results support the use ofliraglutide to achieve glycaemic goals in patients with inadequate control on metformin.

The efficacy of 1.2 mg and 1.8 mg liraglutide in our study exceeded that reported in the phase 3 LEAD-2 study.[16] Although baseline HbA1c was similar in both studies, most patients entering LEAD-2 were receiving metformin and a sulphonylurea, and switched to metformin monotherapy during the run-in period. In our study, participants received metformin monotherapy before inclusion and baseline treatment was not changed. This protocol replicates usual clinical practice, in which new antidiabetic drugs are typically added to, rather than replacing, existing treatment. The reduction in HbA1c with sitagliptin in our study was similar, if not higher, than in previous trials.[10,13]

Greater HbA1c reduction with liraglutide versus sitagliptin is probably due to pharmacological concentrations of free (non-albumin-bound) liraglutide, whereas physiological concentrations of endogenous GLP-1 and GIP are achieved with sitagliptin. Although DPP-4 inhibitors increase active GLP-1 concentrations by two or three times the concentrations at baseline, [21] the stimulation of GLP-1 receptor activity with liraglutide is estimated to be several times higher than with DPP-4 inhibitors."[22] The long half-life of liraglutide (about 13 h) might also contribute to increased efficacy.[23] Sitagliptin has a similar pharmacokinetic half-life to liraglutide (about 12 h),[24] but the increase in endogenous GLP-1 concentrations with DPP-4 inhibitors occurs mainly after meals. Thus, fasting concentrations of active GLP-1 remain fairly low overnight, so reductions in fasting plasma glucose concentrations with sitagliptin are low compared with liraglutide.[24] Our results are similar to preliminary data presented from the 26-week randomised DURATION-2 trial,[25] in which long-acting exenatide taken once a week reduced HbA1c by 1.55%, compared with 0.92% with sitagliptin and 1.23% with pioglitazone. We did not identify any other long-term comparisons of GLP-1 receptor agonists with DPP-4 inhibitors in a search of published reports.

Liraglutide reduced bodyweight more than sitagliptin did. This result is probably due to increased stimulation of the GLP-1 receptor by liraglutide. We recorded mean reductions in bodyweight with liraglutide that were similar to those in other phase 3 liraglutide trials.[9,16] A meta-analysis of the six phase 3 LEAD trials of 2739 participants receiving liraglutide showed that decreases in HbA1c were independent of weight loss.[26] By contrast, DPP-4 inhibitors have usually had negligible weight effects.[6,10,14] Since a slight weight reduction occurred with sitagliptin and efficacy was similar to that in other studies, [6,10,14] we believe that trial conditions were not biased against sitagliptin.

Liraglutide resulted in significant improvements in C-peptide concentration, HOMA index of β-cell function, and proinsulin-to-insulin ratio compared with sitagliptin. This finding could be indicative of sustained concentrations of liraglutide during a 24-h period, especially during the fasting state. 1.8 mg liraglutide also seemed to be associated with significantly greater increase in treatment satisfaction than did sitagliptin, despite the fact that liraglutide was given by injection and sitagliptin was taken orally. This result is important because increased treatment satisfaction is associated with increased treatment adherence and improved clinical outcomes,[27] but the effect of improved treatment satisfaction with liraglutide needs to be confirmed in clinical practice.

Overall, both liraglutide and sitagliptin were well tolerated. Most adverse events were mild or moderate, and serious adverse events were mostly judged to be unrelated to trial drugs. As expected, the frequency of nausea was higher with liraglutide than with sitagliptin, which is consistent with results from previous trials with liraglutide, other GLP-1 receptor agonists, and DPP-4 inhibitors.[8-18] For patients on liraglutide, most episodes of nausea occurred early in the trial with few withdrawals; by later weeks, the occurrence of nausea was similar to that with sitagliptin. Phase 3 studies for exenatide and sitagliptin predate concerns about pancreatitis, but cases have been reported in postmarketing surveillance.[28-29] Although no pancreatitis occurred in this study, cases were reported in the liraglutide LEAD studies.[9,12,15,16] The potential association between incretins and acute pancreatitis remains to be established. Recent epidemiological studies suggest that the risk of pancreatitis with incretin-based therapies is no higher than that with other diabetes treatments, or from the risk in the general population with type 2 diabetes mellitus.[30]

Unlike previous studies with liraglutide,[9,12,15] no significant decreases in systolic blood pressure were noted. We have no clear explanation for this discrepancy. However, the small increases in heart rate and the absence of clinically relevant change in calcitonin concentrations are consistent with previous trials with liraglutide.[9,12,15,16]

Last observation carried forward is a common method to impute missing data, and was used in previous phase 3 liraglutide trials,[9,12,15,16] and in our comparison of liraglutide with sitagliptin. This method has been criticised, but it is transparent in the context of diabetes trials.[31] In our study, we additionally analysed the primary endpoint with the full analysis set without

imputation and with the per-protocol dataset; the conclusions were unchanged from those with the full analysis set with imputation. The open-label design is unlikely to have affected measures of glycaemic control, β-cell function, and the lipid profile, but could have affected investigator and participant perception of treatment. For example, participants could have had different expectations of the specific effects of liraglutide or sitagliptin on bodyweight, which might have affected adherence to lifestyle recommendations. However, predictions of the overall extent or direction of such effects are difficult. Patients enrolled in the study were predominantly white, and all were from Europe, the USA, and Canada, so further research is needed to assess whether findings can be extrapolated to other patient populations. Since the study was 26 weeks in duration, additional research is underway to assess whether treatment differences are maintained long term.

Contributors

REP participated in the study design, enrolled patients, reviewed and interpreted the clinical trial report and data, and prepared the first draft and edited subsequent revisions of the report. MN, TB, EM, RC, SF, and MD were investigators, and they participated in the interpretation of data, and in review of the draft report and subsequent revisions of the report. RES participated in the study design, did the statistical analyses, and contributed to preparation and revision of the report. ABT was International Medical Director for the trial, and she participated in planning of analyses, data interpretation, and drafting of the report. All authors attended a writers' meeting for this report, and approved the final version.

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Conflicts of interest

REP's institntion has received research grants from Eli Lilly, GlaxoSmithKline, Mannkind, Merck, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi-Aventis, and Takeda. REP has received fees for consultancy and honoraria for membership in advisory boards from AstraZeneca, Bristol-Myers Squibb, Eisai, GlaxoSmithKline, Glenmark, Merck, Novartis, Novo Nordisk, Roche, and Takeda; honoraria for participation in speakers' bureaux, and travel and accommodation expenses to attend an investigators' meeting from Novo Nordisk; and holds stock in Novartis. MN has received research grants to his institntion from Merck Sharp & Dohme, and Novo Nordisk; has received honoraria, travel and accommodation expenses, and payment for educational presentations from Novo Nordisk and Merck Sharpe & Dohme; has been a board member for Novo Nordisk and Merck Sharpe & Dohme; and has received payment for for travel, accommodation, and an honorarium to attend an investigators' meeting from Novo Nordisk. TB has received research support from Amylin Pharmaceuticals and Novo Nordisk; has attended speakers' bureaux for Amylin Pharmaceuticals and Novo Nordisk; and has received payment for travel, accommodation, and an honorarium to attend an investigators' meeting from Novo Nordisk. EM has has received research support from Novo Nordisk; has been a consultant for Merck Sharp & Dohme, Novartis, Novo Nordisk, and Sanofi-Aventis; has received honoraria for lectnres from Eli lilly, Merck Sharp & Dohme, Novartis, and Novo Nordisk; has received expenses for attendance at scientific meetings from Almirall, GlaxoSmithKline, Novo Nordisk, and Sanofi-Aventis: and has received the costs of participation in the clinical trial that is the subject of this publication, with payment for travel and accommodation to attend an investigators' meeting from Novo Nordisk. RC is a paid employee of the non-profit International Diabetes Center (Park Nicollet, St Louis Park, MN, USA), and all honoraria, speaking fees, consulting fees, and research and educational support have been paid directly to the International Diabetes Center, with no personal payments to RC. On behalf of his institntion, RC has been a consultant for Novo Nordisk, Bayer, Roche, and CeQur; has received honoraria for speaking and consultancy from Roche and Novo Nordisk; has received payment for educational presentations from Lifescan, Eli Lilly, Merck, and Novartis; has received travel and accommodation expenses from Novo Nordisk, Bayer, Roche, CeQur, Lifescan, Eli Lilly, Merck, and Novartis; has or is principal or co-investigator for sponsored clinical trial research for Amylin, Abbott, Bayer, Daiichi-Sankyo, Edwards Lifesciences, Eli lilly, Dexcom, lifescan, Mannkind, Medtronie, Merck, Novo Nordisk, Quotient Diagnostics, ResMed, Roche, Sanofi-Aventis, and Takeda; and is a board member for Incubatin for Roche Diagnostics. RC's spouse is a physician and medical director with Optum Health, a subdivision of United Health Group. SF has received honoraria, and travel and accommodation expenses for attending an investigators' meeting from Novo Nordisk; has received payment for writing of this report from Novo Nordisk; has been a consultant for Novo Nordisk; and has received payment for educational presentations from Novo Nordisk. ABT and RES are employees of Novo Nordisk, were directly involved in the stndy conduct, and received travel and accommodation expenses from Novo Nordisk to attend an investigators' meeting; ABT's daughter and RES own shares in Novo Nordisk. MD has attended advisory panels for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, and Sanofi-Aventis; has been a consultant for

Novartis; has received grants to her institntion from Eli Lilly, GlaxoSmithKline, and Merck Sharp & Dohme; has received honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, and SanofiAventis; has received payment for educational presentations from Eli Lilly, Novo Nordisk, Sanofi-Aventis, and Merck Sharp & Dohme; and has received payment, and travel and accommodation expenses to attend an investigators' meeting from Eli lilly, Novo Nordisk, and Sanofi-Aventis.

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