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CLINICAL TRIAL

Liraglutide is effective and well tolerated in combination with an oral antidiabetic drug in Japanese patients with type 2 diabetes: A randomized, 52-week, open-label, parallel-group trial

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ABSTRACT

Introduction: The safety and efficacy of liraglutide in combination with an oral antidiabetic drug (OAD) compared with combination of two OADs were assessed in Japanese patients with type 2 diabetes.

Materials and Methods: This was a 52-week, open-label, parallel-group trial in which patients whose type 2 diabetes was inadequately controlled with a single OAD (glinide, metformin, α-glucosidase inhibitor or thiazolidinedione) were randomized 2:1 to either pretrial OAD in combination with liraglutide 0.9 mg/day (liraglutide group; $n = 240$) or pretrial OAD in combination with an additional OAD (additional OAD group; $n = 120$). The primary outcome measure was the incidence of adverse events (AEs).

Results: Overall, 86.3% of patients in the liraglutide group and 85.0% of patients in the additional OAD group experienced AEs; these were similar in nature and severity. Adverse event rates were 361 and 331 per 100 patient-years of exposure, respectively. Confirmed hypoglycemia was rare (seven episodes in two patients on liraglutide, and two in two patients on additional OAD). There were no reported pancreatitis events, and no unexpected safety signals were identified. Mean reductions in glycosylated hemoglobin were significantly greater in the liraglutide group than the additional OAD group [estimated mean treatment difference –0.27% (95% confidence interval (CI) –0.44, –0.09; $P = 0.0026$)]; reductions in mean fasting plasma glucose levels were also greater with liraglutide [estimated mean difference –5.47 mg/dL (–0.30 mmol/L; 95% CI: –10.83, –0.10; $P = 0.0458$)].

Conclusions: Liraglutide was well tolerated and effective as combination therapy with an OAD in Japanese patients with type 2 diabetes.

INTRODUCTION

Type 2 diabetes is a progressive disorder, characterized by insulin resistance at peripheral tissues and relative insulin secretion deficiency[1]. As the disease progresses, monotherapy and then combination therapy might become necessary as an add-on to diet and exercise; glucagon-like peptide 1 (GLP-1) receptor agonists, oral antidiabetic drugs (OADs) and/or insulin are the current intensification options[1,2].

GLP-1 is a hormone that stimulates glucose-dependent insulin secretion and suppresses glucagon secretion[3]. However, endogenous GLP-1 has a very short half-life (1.5 min)[3],

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which limits its therapeutic value. Liraglutide is an analog of human GLP-1 with 97% homology to the endogenous protein[4] and a half-life of 13 h, resulting in a pharmacokinetic profile that is suitable for once-daily dosing[5]. The safety and efficacy of liraglutide have been established through a series of international phase 3 trials [Liraglutide Effect and Action in Diabetes (LEAD)][6–14], as well as two trials in Japan[15–18].

Sulfonylureas (SUs) are the most commonly used OADs in Japan, and the efficacy and safety of liraglutide in combination with a SU has been established in Japanese patients with type 2 diabetes[15]. No other liraglutide combinations have been investigated in phase 3 trials in Japanese patients. However, such trials have been carried out globally, and showed that liraglutide is effective and well tolerated in combination with one or two OADs[7,9,10].

In July 2010, the Japanese Ministry of Health, Labor and Welfare issued a guideline stating that investigational drugs confirmed to be useful in clinical studies that conformed to the guideline could receive a broad indication for 'type 2 diabetes'[19]. Any product having this indication can be used concomitantly with any other approved antihyperglycemic agent that has a different mechanism of action. Thus, the present study was initiated with the objective of assessing the safety and efficacy of liraglutide in combination with OAD options available at the time of designing the trial (glinide, metformin, α-glucosidase inhibitor or thiazolidinedione), vs a combination of two OADs, in patients with type 2 diabetes insufficiently controlled with OAD monotherapy. As stipulated in the Japanese Ministry of Health, Labor and Welfare guideline, the primary end-point of the study was safety, and the study duration was set at 1 year[19]. Glinides, metformin, α-glucosidase inhibitors or thiazolidinediones were selected as the allowed OADs for co-administration with liraglutide. SUs and dipeptidyl peptidase-4 (DPP-4) inhibitors were not included, because concomitant use of liraglutide and SUs was already approved in Japan, and because DPP-4 inhibitors affect the same incretin pathway as liraglutide[20].

MATERIALS AND METHODS

Trial Design and Interventions

This was a 52-week, open-label, randomized, parallel-group trial with an active control (combination therapy with two OADs), designed to evaluate the safety and efficacy of liraglutide in combination with an OAD (glinide, metformin, α-glucosidase inhibitor or thiazolidinedione) in patients with type 2 diabetes. It was carried out at 36 sites in Japan between January 2012 and April 2013.

Patients treated previously with one OAD were randomized to liraglutide (0.9 mg/day) add-on therapy (liraglutide group) or to add-on therapy with another OAD (additional OAD group) in a 2:1 ratio, using an Interactive Voice/Web Response Service. At randomization, patients were stratified according to the type of pretrial OAD. It was required that the total daily dose and type of pretrial drug should have remained unchanged for ≥8 weeks before screening.

Patients received their pretrial OAD in combination with liraglutide, or their pretrial OAD in combination with an additional OAD with a mechanism of action different from the pretrial OAD (within the approved combination-use labeling in Japan). The type, dosage and administration of the additional OAD were chosen by the investigator within approved labeling. The additional OAD used could be a DPP-4 inhibitor, SU, glinide, metformin, α-glucosidase inhibitor or thiazolidinedione.

Patients in the liraglutide group injected themselves subcutaneously with liraglutide once daily. The starting dose was 0.3 mg/day; after 1 week, this was escalated to 0.6 mg/day, and after a further week, to 0.9 mg/day.

Participants

The study included male and female Japanese patients aged ≥20 years, with type 2 diabetes for at least 6 months, glycosylated hemoglobin (HbA1c) levels of 7.0–10.0% (both inclusive) and body mass index of <40.0 kg/m^2. All participants were receiving treatment with OAD monotherapy (glinide, metformin, α-glucosidase inhibitor or thiazolidinedione) within approved Japanese labeling, as well as diet and exercise therapy. Patients were excluded if they had used any of the following within the past 12 weeks: a GLP-1 receptor agonist, a DPP-4 inhibitor or insulin. Other exclusion criteria included personal history of non-familial medullary thyroid carcinoma, family or personal history of multiple endocrine neoplasia type 2 or familial medullary thyroid carcinoma, malignant tumor (either known or previous and strongly suspected of recurrence), history of chronic pancreatitis or idiopathic acute pancreatitis, calcitonin ≥160 pg/mL (radioimmunoassay-2 method), or contraindications to liraglutide or any of the OADs (according to Japanese labeling). Patients with recurrent severe hypoglycemia, hypoglycemia unawareness or hospitalization for diabetic ketoacidosis during the previous 6 months were also excluded.

Informed consent was obtained in advance of any trial-related activities. The protocol was reviewed by the Japanese authority according to local regulations, and reviewed and approved by an institutional review board. The trial is registered with clinicaltrials.gov (NCT01512108) and the Japanese Clinical Trials Registry (JapicCTI-121744), and was carried out in accordance with the Declaration of Helsinki[21] and the International Conference on Harmonization Good Clinical Practice[22].

End-Points and Assessments

The primary end-point was the incidence of adverse events (AEs) during 52 weeks. The nature, severity and relationship to trial products of all AEs were recorded (relationship to trial product was judged by investigator). A treatment-emergent AE was defined as an event with an onset date on or after the first day of exposure to randomized treatment (liraglutide or additional OAD) and no later than 7 days after the last day of randomized treatment.

Secondary safety end-points included the number of hypoglycemic episodes during 52 weeks and changes from baseline in vital signs (blood pressure and pulse rate). Hypoglycemia was classified according to the American Diabetes Association definition (severe, documented symptomatic, asymptomatic, probable symptomatic and relative)[23] with the addition of a minor category. Minor hypoglycemia (symptomatic or asymptomatic) was defined as plasma glucose <56 mg/dL (3.1 mmol/L) or blood glucose <50 mg/dL (2.8 mmol/L). Collectively, severe and minor hypoglycemic episodes were referred to as "confirmed" hypoglycemic episodes.

Secondary efficacy end-points were assessed after 52 weeks of treatment. These included change from baseline in HbA1c, change from baseline in fasting plasma glucose (FPG), patients achieving target HbA1c <7.0%, change from baseline in bodyweight and change from baseline in β-cell function [homeostasis model assessment (HOMA)-B, and proinsulin:insulin and proinsulin:C-peptide ratios]. Seven-point self-measured plasma glucose (SMPG) profiles were also assessed (change from baseline in mean plasma glucose and in mean prandial plasma glucose increment). Self-monitoring of blood glucose (SMBG) was carried out with a glucose meter, and converted to plasma values (SMPG).

Statistical Analysis

The necessary sample size (360 patients randomized 2:1 to receive either liraglutide 0.9 mg or additional OAD) was determined based on the requirements of the Japanese Ministry of Health, Labor and Welfare Guideline for Clinical Evaluation of Oral Hypoglycemic Agents[19]. Randomization was stratified according to the type of pretrial OAD, with a requirement for 90 patients (60 in the liraglutide 0.9 mg group and 30 in the additional OAD group) to be included in each OAD stratum. The number of patients was determined such that at least 50 patients would complete the 52-week treatment with liraglutide 0.9 mg in combination with each OAD, assuming a dropout rate of 15%, in accordance with the guideline[19].

The full analysis set included all randomized patients who received at least one dose of trial products; evaluation followed the intention-to-treat principle, with patients contributing 'as randomized'. The safety analysis set included all patients receiving at least one dose of trial product, with patients contributing 'as treated'. Analyses were based on full analysis set for efficacy end-points and on the safety analysis set for safety end-points. For all end-points, the last observation carried forward approach was used for patients with at least one valid post-baseline measurement.

For the primary end-point (incidence of AEs), the number of patients experiencing an event, the percentage of patients with at least one event, the number of events and the event rate per 100 patient-years of exposure (PYE) are presented.

For change from baseline in blood pressure and pulse rate after 52 weeks of treatment, 95% confidence intervals (CIs) for the mean difference (liraglutide group minus additional OAD group) were calculated based on an analysis of variance (ANOVA) model, with treatment group and type of pretrial OAD as fixed effects, and the corresponding baseline value as a covariate. Secondary efficacy end-points (except for patients achieving target HbA1c <7.0%) were also analyzed using an ANOVA model, with treatment group and type of pretrial OAD as fixed effects, and the corresponding baseline value as a covariate. The estimated mean differences with corresponding 95% CIs are provided together with the two-sided *P*-values. Observed end-of-treatment values are given as mean ± standard deviation. End-points for β-cell function were log-transformed before analysis. For the analysis of patients achieving target HbA1c <7.0%, a logistic regression model was used with treatment group and type of pretrial OAD as fixed effects, and HbA1c at baseline as a covariate. The estimated odds ratio with corresponding 95% CI is shown, together with the two-sided *P*-value.

RESULTS

Demographics

A total of 363 patients were randomized, of whom three in the liraglutide group were withdrawn before being exposed to the trial product (Figure 1). A total of 360 patients received at least one dose: 240 in the liraglutide group and 120 in the additional OAD group. The withdrawal rate was comparable between the two treatment groups (9.1% in the liraglutide group; 7.5% in the additional OAD group).

The number of patients withdrawing because of AEs was similar for both treatment groups [nine patients (3.8%) and four patients (3.3%) for the liraglutide and placebo group, respectively].

In general, the demographics and baseline characteristics were similar (Table 1). In the additional OAD group, the OAD added after randomization was either a DPP-4 inhibitor (n = 51), metformin (n = 30), α-glucosidase inhibitor (n = 16), SU (n = 14), thiazolidinedione (n = 5) or glinide (n = 4).

Safety

No new safety concerns were identified in either treatment group during the study. The primary end-point was the incidence of AEs, and comparable proportions of patients reported AEs in the liraglutide (86.3%) and additional OAD (85.0%) groups (Table 2). The majority of AEs were mild in severity. The overall AE rate was similar between the two groups (361 and 331 events per 100 PYE in the liraglutide and additional OAD groups, respectively; Table 2). The relationship to the trial product was judged only for liraglutide, and most AEs were considered unlikely to be related by the investigator.

Gastrointestinal disorders appeared more common in the liraglutide group than in the additional OAD group (50.8% vs 34.2%, 89 vs 75 events per 100 PYE, respectively; Table 2). The most frequently reported gastrointestinal AE in both treatment groups was constipation. Gastrointestinal AEs occurred most frequently within the first 4 weeks of the treatment period (data not shown), particularly in the liraglutide group, but during the

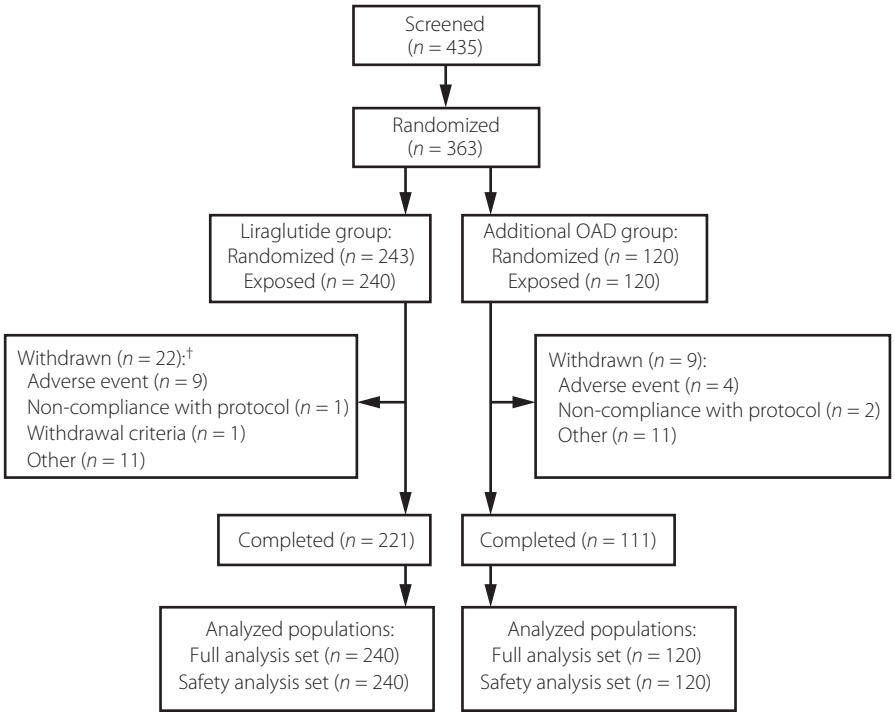

Figure 1 | Participant flow during the trial. †Three patients in the liraglutide group were withdrawn after randomization, but before exposure to the trial product (consent withdrawal $n = 1$; randomization in error $n = 1$; non-compliance $n = 1$). The remainder were withdrawn after exposure to at least one dose. OAD, oral antidiabetic drug.

Table 1 | Participant demographics and baseline characteristics

	Liraglutide ($n = 240$)	Additional OAD ($n = 120$)	Total ($n = 360$)
Male, *n* (%)	182 (75.8)	80 (66.7)	262 (72.8)
Age (years)	59.6 (11.6)	59.2 (10.2)	59.5 (11.1)
Bodyweight (kg)	69.4 (14.2)	68.2 (13.6)	69.0 (14.0)
BMI (kg/m^2)	25.7 (4.2)	25.5 (3.7)	25.7 (4.1)
Duration of diabetes (years)	7.80 (5.77)	8.47 (6.55)	8.02 (6.04)
FPG (mg/dL)	156 (29)	161 (33)	158 (30)
HbA1c (%)	8.1 (0.8)	8.1 (0.8)	8.1 (0.8)
Pretrial OAD, *n* (%)			
α-GI	63 (26.3)	30 (25.0)	93 (25.8)
Glinide	58 (24.2)	31 (25.8)	89 (24.7)
Metformin	61 (25.4)	31 (25.8)	92 (25.6)
Thiazolidinedione	58 (24.2)	28 (23.3)	86 (23.9)

Data are mean (standard deviation) unless otherwise stated. α-GI, α-glucosidase inhibitor; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; OAD, oral antidiabetic drug.

remainder of the treatment period gastrointestinal AEs occurred sporadically in both groups, and no specific occurrence patterns were observed. Nasopharyngitis was the most frequently reported AE, when categorized according to preferred terms, and the rates and percentages of patients experiencing these events were similar in both groups (37.1 and 39.2% in the liraglutide and additional OAD groups, respectively).

Based on a predefined MedDRA PT search, a total of 15 injection-site reactions were identified in 12 patients (5.0%) in the liraglutide group, but all of these events were non-serious and mild in severity.

The incidence of serious AEs was low in both groups (five and nine events per 100 PYE in the liraglutide and additional OAD groups, respectively). A total of 13 patients were withdrawn from the trial owing to AEs, of whom nine were in the liraglutide group and four were in the additional OAD group. One death was reported in the liraglutide group: a malignant lung neoplasm that was diagnosed after 5 months of exposure to the trial product. This was considered unlikely to be related to the trial product by the investigator.

There were no reported events of pancreatitis or suspicion of pancreatitis. For both amylase and lipase, the mean values at baseline and after 52 weeks were within the reference ranges (37–125 U/L for amylase; 11–53 U/L for lipase). After 52 weeks of treatment, geometric mean amylase levels (68 U/L at baseline) appeared higher in the liraglutide group than in the additional OAD group (74.3 U/L vs 70.8 U/L, respectively). Similarly, geometric mean lipase levels (36 U/L at baseline) appeared higher with liraglutide than with additional OAD (49.3 U/L vs 37.6 U/L, respectively). Changes in calcitonin were

Table 2 | Summary of treatment-emergent adverse events (safety analysis set)

	Liraglutide (n = 240)			Additional OAD (n = 120)		
	n (%)	No. events	Event rate per 100 PYE	n (%)	No. events	Event rate per 100 PYE
All AEs	207 (86.3)	817	361	102 (85.0)	380	331
Serious AEs	11 (4.6)	11	5	10 (8.3)	10	9
Severity						
Severe	4 (1.7)	5	2	2 (1.7)	2	2
Moderate	22 (9.2)	31	14	9 (7.5)	10	9
Mild	207 (86.3)	781	345	102 (85.0)	368	321
Nasopharyngitis	89 (37.1)	135	60	47 (39.2)	85	74
Influenza	8 (3.3)	8	4	6 (5.0)	6	5
Constipation	44 (18.3)	48	21	12 (10.0)	13	11
Nausea	31 (12.9)	33	15	4 (3.3)	4	3
Diarrhea	20 (8.3)	25	11	9 (7.5)	10	9
Abdominal discomfort	19 (7.9)	21	9	1 (0.8)	1	1
Dental caries	7 (2.9)	7	3	6 (5.0)	6	5
Diabetic retinopathy	21 (8.8)	22	10	16 (13.3)	16	14
Cataract	8 (3.3)	8	4	8 (6.7)	8	7
Headache	12 (5.0)	14	6	4 (3.3)	4	3
Back pain	13 (5.4)	14	6	3 (2.5)	3	3

AE, adverse event; GI, gastrointestinal; OAD, oral antidiabetic drug; PYE, patient-years of exposure.

small in both treatment groups, and no apparent differences were observed between groups.

Seven confirmed hypoglycemic episodes were reported in two patients in the liraglutide group, and two episodes in two patients in the additional OAD group. Only one nocturnal confirmed hypoglycemic episode was reported (in the liraglutide group), and there were no recorded severe hypoglycemic episodes in the present trial.

Estimated mean changes from baseline to week 52 in systolic and diastolic blood pressure were −4.00 mmHg and −1.44 mmHg in the liraglutide group, and −3.91 mmHg and −1.64 mmHg in the additional OAD group, respectively. Estimated between-group differences were small and not statistically significant [systolic blood pressure −0.10 mmHg (95% CI −2.54, 2.35; P = 0.9384); diastolic blood pressure 0.20 mmHg (95% CI −1.55, 1.95; P = 0.8246)]. With regard to pulse rates, there were estimated mean increases from baseline to week 52 of 6.2 and 2.4 b.p.m. in the liraglutide and additional OAD groups, respectively; the estimated mean treatment difference between groups was 3.8 b.p.m. (95% CI 1.9, 5.8; P = 0.0001). No apparent developments in electrocardiography were noted.

Efficacy

After 52 weeks of treatment, the observed mean (standard deviation) HbA1c was 6.8% (1.0%) with liraglutide and 7.1% (0.8%) with additional OAD (last observation carried forward imputed data). A significantly greater mean reduction in HbA1c was observed in the liraglutide group (−1.21%) than in the additional OAD group (−0.94%; Figure 2; Table 3). The estimated mean treatment difference was −0.27% (95% CI −0.44, −0.09; P = 0.0026) in favor of liraglutide.

In a logistic regression model, the estimated proportion of patients achieving HbA1c <7.0% at 52 weeks was 67.6% in the liraglutide group and 44.8% in the additional OAD group (Table 3). The proportion of patients achieving this target was statistically significantly higher in the liraglutide group [estimated odds ratio 2.57 (95% CI 1.54, 4.28; P = 0.0003)].

After 52 weeks of treatment, the observed mean FPG level (standard deviation) was 129 mg/dL [30 mg/dL; 7.17 mmol/L (1.68 mmol/L)] in the liraglutide group and 138 mg/dL [28 mg/dL; 7.63 mmol/L (1.58 mmol/L)] in the additional OAD group. The reduction from baseline was greater with liraglutide [−27.8 mg/dL (−1.55 mmol/L)] than with additional OAD [−22.4 mg/dL (−1.24 mmol/L); Table 3]; the estimated mean treatment difference was −5.47 mg/dL (−0.30 mmol/L; 95% CI −10.83, −0.10; P = 0.0458).

According to measurements of seven-point SMPGs, converted from SMBG, the estimated mean treatment difference in mean glucose was −9.8 mg/dL (−0.55 mmol/L; 95% CI −16.9, −2.8; P = 0.0066) for the liraglutide group compared with the additional OAD group (Table 3). No significant difference was identified between liraglutide and additional OAD in terms of mean prandial increment in SMPG values across all meals, with an estimated mean treatment difference (liraglutide minus additional OAD) of 1.9 mg/dL (0.11 mmol/L; 95% CI −4.8, 8.7; P = 0.5768).

After 52 weeks of treatment, patients in the liraglutide group had significantly higher HOMA-B [estimated treatment ratio

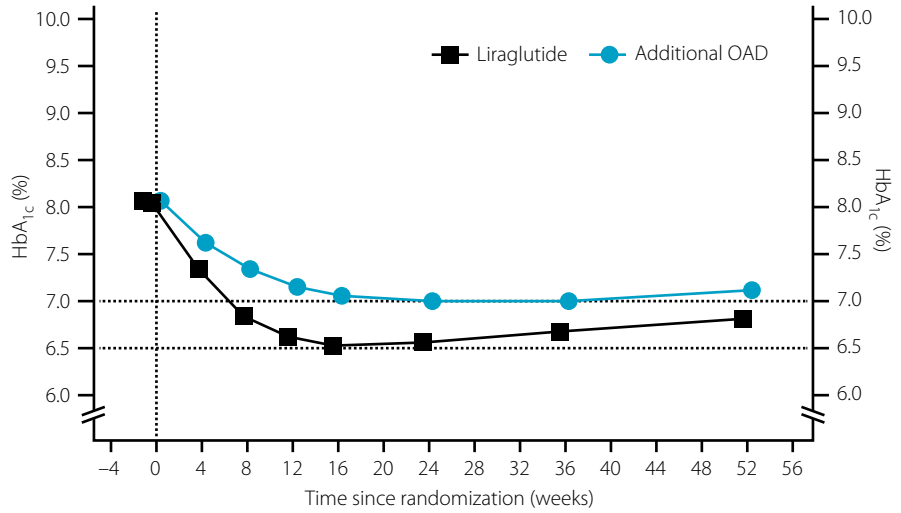

Figure 2 | Mean glycosylated hemoglobin by treatment week (full analysis set). Last observation carried forward imputed data. HbA1c, glycosylated hemoglobin; OAD, oral antidiabetic drug.

Table 3 | Summary of efficacy end-points

End-point (52 weeks)	Liraglutide (n = 240)	Additional OAD (n = 120)	Treatment comparison (95% CI)	P-value
Change in HbA1c (%)	–1.21	–0.94	–0.27 (–0.44, –0.09)‡	0.0026
Patients achieving HbA1c <7.0% (%)	67.6	44.8	2.57 (1.54, 4.28)§	0.0003
Change in FPG (mg/dL)	–27.8	–22.4	–5.47 (–10.83, –0.10)‡	0.0458
Change in mean plasma glucose† (mg/dL)	–40.6	–30.8	–9.8 (–16.9, –2.8)‡	0.0066
HOMA-B (%)	45.24	35.28	1.28 (1.16, 1.42)¶	<0.0001
Proinsulin:insulin ratio (%)	31.36	37.92	0.83 (0.74, 0.92)¶	0.0006
Proinsulin:C-peptide ratio	0.024	0.030	0.813 (0.742, 0.892)¶	<0.0001
Change in bodyweight (kg)	–0.85	–0.50	–0.35 (–0.99, 0.29)‡	0.2766

CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; HOMA-B, homeostasis model assessment B; OAD, oral antidiabetic drug. †Seven-point self-measured plasma glucose. Treatment comparison values are: ‡estimated treatment difference; §estimated odds ratio; ¶estimated treatment ratio.

1.28 (95% CI 1.16, 1.42; $P < 0.0001$)], lower proinsulin:insulin ratio [estimated treatment ratio 0.83 (95% CI 0.74, 0.92; $P = 0.0006$)] and lower proinsulin:C-peptide ratio [estimated treatment ratio 0.813 (95% CI 0.742, 0.892; $P < 0.0001$)] compared with the additional OAD group (Table 3).

Patients in both groups experienced small estimated weight losses at week 52 (liraglutide –0.85 kg; additional OAD –0.50 kg). There was no significant difference between the groups [estimated mean treatment difference –0.35 kg (95% CI –0.99, 0.29; $P = 0.2766$); Table 3]. The small weight loss observed in this study might be a result of a lower baseline body mass index (25 vs 30–35 kg/m^2 in non-Japanese patients enrolled in international trials).

DISCUSSION

This was a 52-week, open-label, randomized, parallel-group trial with an active control (combination therapy with two OADs) to evaluate the safety and efficacy of liraglutide in addition to an OAD in Japanese patients with type 2 diabetes inadequately controlled with one OAD. The primary objective was to evaluate the safety of once-daily liraglutide (0.9 mg/day) in combination with an OAD (either glinide, metformin, α-glucosidase inhibitor or thiazolidinedione). In general, liraglutide was well tolerated, and no new safety signals were identified. Furthermore, the safety profile for liraglutide was consistent with previous findings from international trials, including those carried out in Japan, in which liraglutide was studied as a monotherapy[8,17], or in combination with metformin[7,24], a SU[6,15], metformin, a SU or both[11], metformin plus thiazolidinedione[9], or metformin plus an SU[10].

Gastrointestinal effects are commonly reported during treatment with GLP-1 receptor agonists, particularly in the treatment initiation period[25]. In the present study, gastrointestinal AEs were reported in both treatment groups, but the occurrence was higher with liraglutide than with additional OAD.

However, the difference was mostly because of greater numbers of gastrointestinal AEs during the first 4 weeks of treatment. Stepwise dose escalation was applied to mitigate this issue, in accordance with the usual administration of liraglutide.

Mean amylase and lipase values were slightly increased in the liraglutide group by week 52. However, the increases observed were consistent with previous findings[26], and mean values at week 52 were within the reference ranges and thus not considered clinically relevant. No pancreatitis events were identified.

In the present study, rates of confirmed hypoglycemic episodes were low in both groups. The mechanism of action of liraglutide is glucose-dependent, and hence rates of hypoglycemia are typically much lower than with, for example, SUs[25,27].

Liraglutide in combination with an OAD was found to improve glycemic control more effectively than the combination of two OADs. A statistically significantly greater reduction in HbA1c was observed in the liraglutide group than in the additional OAD group. The FPG and SMPG profiles supported this finding.

Although the HbA1c reduction with liraglutide was clinically relevant, relatively low mean baseline HbA1c values (8.1% in both groups) might explain the modest treatment difference in HbA1c (0.27% in favor of liraglutide). Furthermore, more patients in the liraglutide group achieved the HbA1c target of <7.0%. Considering the small increase in mean HbA1c level in the liraglutide group compared with the additional OAD group during the second half of the trial period (Figure 2), the management of patients who had achieved the HbA1c target possibly became less aggressive (e.g., to reduce the risk of hypoglycemia with the pretrial OAD); however, there are no data to confirm this.

The reductions in HbA1c with liraglutide seen in the present study were relative to an additional OAD group receiving various different comparator compounds. However, direct comparisons from other trials have shown that liraglutide significantly reduces HbA1c relative to SUs (as monotherapy)[8,17], sitagliptin (as an add-on to metformin)[24], rosiglitazone (as an add-on to SU)[6] and exenatide (as an add-on to metformin, SU or both)[11]. The greater effect of liraglutide, compared with other therapies, on HbA1c levels could relate to its broad physiological effects, including stimulation of insulin secretion and reduction of glucagon secretion. Although the maximum dose of liraglutide in Japan (0.9 mg/day) is half that in Europe and the USA (1.8 mg/day), the efficacy observed in the present study was comparable with that seen in trials carried out in the West.

Furthermore, measures of β-cell function were improved in the liraglutide group relative to the additional OAD group. This is consistent with previous findings from a phase 3 study of liraglutide in combination with a SU in Japanese patients[18]. Similarly, in animal models, GLP-1 and GLP-1 receptor agonists have been shown to preserve or even improve β-cell function[28–32]. However, further investigation will be required to elucidate the clinical importance of this observation.

There were some limitations to the present work. For practical and ethical reasons, an open-label design was chosen, which meant that treatment was not blinded. The study lasted for 52 weeks, and hence the durability of the results beyond that time in Japanese patients is not known. Furthermore, there might be selection bias in patients who volunteer for a study, particularly one that involves an injectable drug; this should be considered when generalizing these results to a larger/different population. Finally, data from the present study cannot be extrapolated to young patients (<20 years-of-age) because these were excluded from the trial.

We conclude that the data in Japanese patients (liraglutide 0.9 mg/day) support those reported in other nationalities and ethnicities in finding that liraglutide is well tolerated and effective as combination therapy with an OAD in patients with type 2 diabetes. Reductions in HbA1c were significantly greater with liraglutide than with two OADs in combination. Overall, the data suggest that liraglutide plus an OAD might be more effective than a combination of two OADs in Japanese patients with type 2 diabetes, with a safety profile consistent with previous findings.

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DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Inzucchi SE, Bergenstal RM, Buse JB, *et al.* Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2012; 35: 1364–1379.
2. Japan Diabetes Society. Treatment Guide for Diabetes: 2012–2013. Available at: http://www.jds.or.jp/common/fckeditor/editor/filemanager/connectors/php/transfer.php?file=/uid000025_54726561746D656E745F47756964655F666F725F44696162657465735F323031322D323031332E706466. Accessed March 2014.
3. Holst JJ. The physiology of glucagon-like peptide 1. *Physiol Rev* 2007; 87: 1409–1439.
4. Knudsen LB, Nielsen PF, Huusfeldt PO, *et al.* Potent derivatives of glucagon-like peptide-1 with pharmacokinetic properties suitable for once daily administration. *J Med Chem* 2000; 43: 1664–1669.
5. Agerso H, Jensen LB, Elbrond B, *et al.* The pharmacokinetics, pharmacodynamics, safety and tolerability of NN2211, a new long-acting GLP-1 derivative, in healthy men. *Diabetologia* 2002; 45: 195–202.
6. Marre M, Shaw J, Brändle M, *et al.* Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with type 2 diabetes (LEAD-1 SU). *Diabet Med* 2009; 26: 268–278.
7. Nauck M, Frid A, Hermansen K, *et al.* Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. *Diabetes Care* 2009; 32: 84–90.
8. Garber A, Henry R, Ratner R, *et al.* Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet* 2009; 373: 473–481.
9. Zinman B, Gerich J, Buse JB, *et al.* Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). *Diabetes Care* 2009; 32: 1224–1230.
10. Russell-Jones D, Vaag A, Schmitz O, *et al.* Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. *Diabetologia* 2009; 52: 2046–2055.
11. Buse JB, Rosenstock J, Sesti G, *et al.* Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet* 2009; 374: 39–47.
12. Nauck M, Frid A, Hermansen K, *et al.* Long-term efficacy and safety comparison of liraglutide, glimepiride and placebo, all in combination with metformin in type 2 diabetes: 2-year results from the LEAD-2 study. *Diabetes Obes Metab* 2013; 15: 204–212.
13. Garber A, Henry RR, Ratner R, *et al.* Liraglutide, a once-daily human glucagon-like peptide 1 analogue, provides sustained improvements in glycaemic control and weight for 2 years as monotherapy compared with glimepiride in patients with type 2 diabetes. *Diabetes Obes Metab* 2011; 13: 348–356.
14. Buse JB, Sesti G, Schmidt WE, *et al.* Switching to once-daily liraglutide from twice-daily exenatide further improves glycemic control in patients with type 2 diabetes using oral agents. *Diabetes Care* 2010; 33: 1300–1303.
15. Kaku K, Rasmussen MF, Clauson P, *et al.* Improved glycaemic control with minimal hypoglycaemia and no weight change with the once-daily human glucagon-like peptide-1 analogue liraglutide as add-on to sulphonylurea in Japanese patients with type 2 diabetes. *Diabetes Obes Metab* 2010; 12: 341–347.
16. Kaku K, Rasmussen MF, Nishida T, *et al.* Fifty-two-week, randomized, multicenter trial to compare the safety and efficacy of the novel glucagon-like peptide-1 analog liraglutide vs glibenclamide in patients with type 2 diabetes. *J Diabetes Investig* 2011; 2: 441–447.
17. Seino Y, Rasmussen MF, Nishida T, *et al.* Efficacy and safety of the once-daily human GLP-1 analogue, liraglutide, vs glibenclamide monotherapy in Japanese patients with type 2 diabetes. *Curr Med Res Opin* 2010; 26: 1013–1022.
18. Seino Y, Rasmussen MF, Nishida T, *et al.* Glucagon-like peptide-1 analog liraglutide in combination with sulfonylurea safely improves blood glucose measures vs sulfonylurea monotherapy in Japanese patients with type 2 diabetes: results of a 52-week, randomized, multicenter trial. *J Diabetes Investig* 2011; 2: 280–286.
19. Japanese Ministry of Health, Labor and Welfare. Guideline for Clinical Evaluation of Oral Hypoglycemic Agents, 9 July 2010. Available at: http://www.pmda.go.jp/kijunsakusei/file/guideline/new_drug/keikou-kettokoukayaku_en.pdf. Accessed May 2014.
20. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 2006; 368: 1696–1705.
21. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. Last amended by the 59th WMA General Assembly, Seoul 2008.

22. ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6 (R1), Step 4, dated 10 June 1996.
23. Seaquist ER, Anderson J, Childs B, *et al.* Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care* 2013; 36: 1384–1395.
24. Pratley RE, Nauck M, Bailey T, *et al.* Liraglutide versus sitagliptin in patients with type 2 diabetes inadequately controlled on metformin: a 26-week, randomised, parallel-group, open-label trial. *Lancet* 2010; 375: 1447–1456.
25. Davies MJ, Kela R, Khunti K. Liraglutide – overview of the preclinical and clinical data and its role in the treatment of type 2 diabetes. *Diabetes Obes Metab* 2011; 13: 207–220.
26. Steinberg W, DeVries JH, Wadden TA, *et al.* Longitudinal monitoring of lipase and amylase in adults with type 2 diabetes and obesity: evidence from two phase 3 randomized clinical trials with the once-daily GLP-1 analog liraglutide. *Gastroenterology* 2012; 142: S850–S851.
27. Nicolucci A, Rossi MC. Incretin-based therapies: a new potential treatment approach to overcome clinical inertia in type 2 diabetes. *Acta Biomed* 2008; 79: 184–191.
28. Farilla L, Hui H, Bertolotto C, *et al.* Glucagon-like peptide-1 promotes islet cell growth and inhibits apoptosis in Zucker diabetic rats. *Endocrinology* 2002; 143: 4397–4408.
29. Rolin B, Larsen MO, Gotfredsen CF, *et al.* The long-acting GLP-1 derivative NN2211 ameliorates glycemia and increases β-cell mass in diabetic mice. *Am J Physiol Endocrinol Metab* 2002; 283: E745–E752.
30. Hui H, Nourparvar A, Zhao X, *et al.* Glucagon-like peptide-1 inhibits apoptosis of insulin-secreting cells via a cyclic 5′-adenosine monophosphate-dependent protein kinase A- and a phosphatidylinositol 3-kinase-dependent pathway. *Endocrinology* 2003; 144: 1444–1455.
31. Li Y, Hansotia T, Yusta B, *et al.* Glucagon-like peptide-1 receptor signaling modulates β-cell apoptosis. *J Biol Chem* 2003; 278: 471–478.
32. Bregenholt S, Møldrup A, Blume N, *et al.* The long-acting glucagon-like peptide-1 analogue, liraglutide, inhibits β-cell apoptosis in vitro. *Biochem Biophys Res Commun* 2005; 330: 577–584.