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ORIGINAL ARTICLE

# 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

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**Aim:** Sulphonylureas (SUs) are often used as first-line treatments for type 2 diabetes in Japan, hence it is important to study new antidiabetic drugs in combination with SUs in Japanese patients.

**Methods:** The efficacy and safety of the once-daily human glucagon-like peptide-1 (GLP-1) analogue liraglutide were compared in 264 Japanese subjects [mean body mass index (BMI) 24.9 kg/m$^2$; mean glycated haemoglobin (HBA1c) 8.4%] randomized and exposed to receive liraglutide 0.6 mg/day (n = 88), 0.9 mg/day (n = 88) or placebo (n = 88) each added to SU monotherapy (glibenclamide, glicazide or glimeprimide) in a 24-week, double-blind, parallel-group trial.

**Results:** The mean change in HBA1c from baseline to week 24 (LOCF) was −1.56 (s.d. 0.84) and −1.46 (s.d. 0.95) with liraglutide 0.9 and 0.6 mg respectively, and −0.40 (s.d. 0.93) with placebo. HBA1c decreased in the placebo group from 8.45 to 8.06%, while liraglutide reduced HBA1c from 8.60 to 7.14%, and from 8.23 to 6.67% at the 0.6 and 0.9 mg doses respectively. Mean HBA1c at week 24 of the two liraglutide groups were significantly lower than the placebo group ($p < 0.0001$ for both). More subjects reached HBA1c <7.0% with liraglutide (0.6 mg: 46.5%; 0.9 mg: 71.3%) vs. placebo (14.8%). Fasting plasma glucose (FPG) levels were significantly improved with liraglutide (difference −1.47 mmol/l and −1.80 mmol/l with 0.6 and 0.9 mg vs. placebo; $p < 0.0001$). Overall safety was similar between treatments: no major hypoglycaemic episodes were reported, while 84/77/38 minor hypoglycaemic episodes occurred in the 0.6 mg/0.9 mg and placebo treatment groups (all in combination with SU), reflecting lower ambient glucose levels. No relevant change in mean body weight occurred in subjects receiving liraglutide (0.6 mg: 0.06 kg; 0.9 mg: −0.37 kg), while mean body weight decreased in subjects receiving placebo (−1.12 kg).

**Conclusions:** The addition of liraglutide to SU treatment for 24 weeks dose-dependently improved glycaemic control vs. SU monotherapy, without causing major hypoglycaemia or weight gain or loss.

**Keywords:** glucagon-like peptide-1, liraglutide, sulphonylurea, type 2 diabetes

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## Introduction

Type 2 diabetes mellitus (T2DM) is a complex disease characterized by beta-cell dysfunction, insulin resistance and deteriorating glycaemic control [1–8]. The impact of these degenerative processes varies among different populations; indeed, differences in the pathophysiology of T2DM among Japanese and Caucasian patients have been well established. Compared with their Caucasian counterparts, for example, Japanese patients have been shown to have less insulin secretory capacity and insulin resistance, and tend to be less obese [1,3–5,9–11].

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Patients typically start treatment for diabetes with oral antidiabetic drugs (OADs) as monotherapy or in combination therapy, but initial improvement in glycaemic control often wanes over time, with a return to deteriorating blood glucose levels and a marked decline in beta-cell function. OAD use is also commonly associated with adverse events, such as weight gain and hypoglycaemia. An optimal treatment for T2DM would improve glycaemic control and beta-cell function while minimizing the risk of hypoglycaemia and preventing weight gain. Such a therapy would further aim to preserve beta-cell function for as long as possible, and perhaps even reverse the course of deterioration. Recently, new therapies targeting the incretin system have become available that fulfil many of the aspects of the 'optimal' diabetes therapy. Glucagon-like peptide-1 (GLP-1) receptor agonists such as liraglutide, a once-daily human GLP-1 analogue, and exenatide are promising new therapy options for patients with T2DM.

GLP-1 receptor agonists mimic the glucoregulatory actions of endogenous GLP-1 and have been shown to achieve effective glycaemic control through sustained improvements in glycaemic control, beta-cell function and weight, with a low risk of hypoglycaemia [12–20]. In T2DM, the insulin secretion response of beta-cells to physiological levels of GLP-1 is impaired [21], but can be restored with high pharmacological levels of native GLP-1 [22] or with a GLP-1 analogue such as liraglutide [23]. A phase 2 trial in Japanese subjects with type 2 diabetes comparing four once-daily doses of liraglutide (0.1, 0.3, 0.6 and 0.9 mg) to placebo has shown that liraglutide monotherapy significantly decreased HBA1c (up to −1.85%) without incurring a single case of hypoglycaemia or antibody development, or any relevant body weight change [24]. Liraglutide has also been shown to provide significant reductions in HBA1c, fasting plasma glucose (FPG), postprandial glucose (PPG) and weight as add-on therapy to the sulphonylurea (SU), glimepiride vs. glimepiride monotherapy in phase 3 trials outside of Japan [12–17].

In Japan, drugs from the SU class are used by 72–78% of all OAD-treated patients [25]. SUs are also a first-line OAD, comprising 61% of the monotherapy market share in Japan [6]; however, prolonged use of SUs may impair beta-cell function. In contrast, liraglutide has been shown to stimulate proliferation and neogenesis of pancreatic beta-cells *in vitro* [26]. As SUs are the most common first-line OAD treatment, and as liraglutide may counteract beta-cell decline, testing the response of patients on SU monotherapy to SU therapy combined with liraglutide is important. Additionally, enhancing SU monotherapy with incretin treatment may benefit Japanese patients with T2DM because of the decreased insulin secretion capacity found in this population.

The present study evaluates the efficacy and safety of two doses of liraglutide (0.6 and 0.9 mg/day) over 24 weeks compared with placebo, in each case as add-on to SU monotherapy.

## Patients and Methods

### Patient Population

Included subjects (n = 264) were Japanese men and women ≥20 years of age with T2DM currently treated with an SU [glibenclamide (1.25–10 mg), glicazide (40–160 mg) or glimepiride (1–6 mg)] for ≥8 weeks, HBA1c levels ranging from 7.0 to <10%, and body mass index (BMI) <35.0 kg/m$^2$. Subjects were excluded if they had been treated with insulin within 12 weeks, were receiving or expecting to receive systemic corticosteroids, or had known hypoglycaemia unawareness or recurrent major hypoglycaemia, impaired renal or hepatic function, significant cardiovascular disease (heart failure, coronary artery disease or uncontrolled hypertension) or non-stabilized proliferative retinopathy or maculopathy.

### Study Design

This was a double-blind, 24-week, three-arm trial. Subjects continued on their current SU monotherapy (glibenclamide, glicazide or glimeprimide) and were randomized to either one of two once-daily liraglutide doses (0.6 or 0.9 mg/day added onto SU; liraglutide groups) or to placebo (placebo group). The trial was part of a 52-week, multicentre, double-blind, randomized, parallel-group trial in which the initial 24-week double-blind period was followed by a 28-week open-label period to assess the long-term safety and efficacy of liraglutide. The trial was performed at 49 centres in Japan, in accordance with the 'Declaration of Helsinki' and with the informed consent of all subjects involved.

A 4-week (±7 day) run-in/screening period preceded randomization (figure 1), after which subjects were stratified according to their pretrial SU therapy. Following randomization, subjects entered a 2-week dose escalation period during which the daily liraglutide doses were uptitrated from 0.3 mg/day (50 µl) to 0.6 mg/day (100 µl) after the first week, with an additional increase to 0.9 mg/day (150 µl) for the

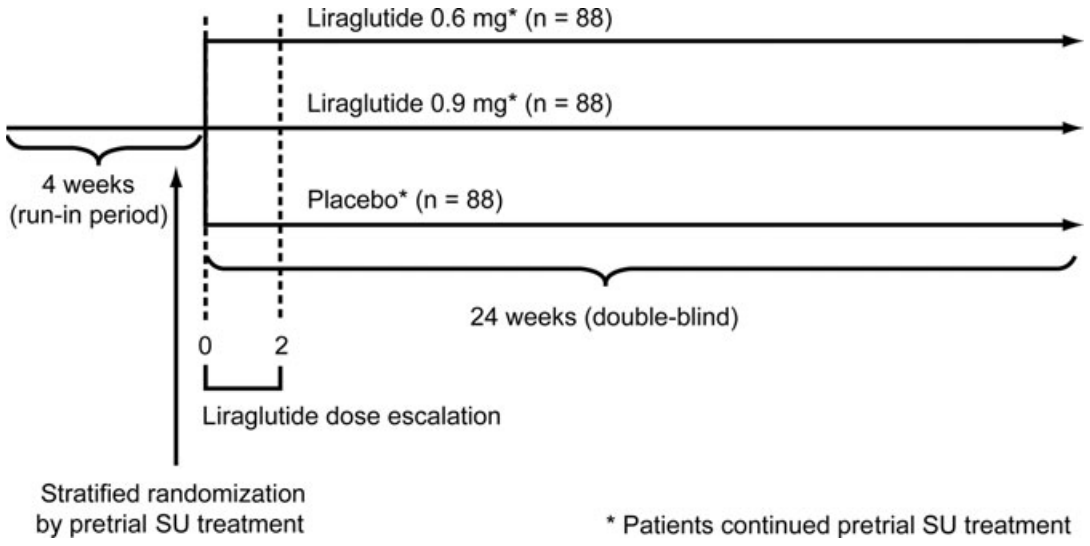


**Figure 1.** Trial design. SU, sulphonylurea.

0.9 mg cohort after the second week. Subjects continued on their current SU therapies throughout the trial. As a rule, there were no changes in SU dose or dosage during the study. During the 22-week maintenance period, liraglutide was injected once daily in the morning or evening subcutaneously into the upper arm, thigh or abdomen.

### Study Measurements

*Efficacy.* The primary endpoint was subjects' HBA1c level at 24 weeks. Secondary endpoints included 7-point self-measured PPG profiles, body weight, FPG, mean PPG, lipid profile and biomarkers for cardiovascular effects. The percentage of subjects reaching HBA1c targets of <7% (*post hoc* analysis) or <6.5% were also analysed.

All analyses were performed by a central laboratory (Mitsubishi Chemical Medience Corporation, Tokyo, Japan) except for the 7-point plasma glucose profile, which subjects performed at home.

*Safety.* Safety endpoints included incidence of hypoglycaemic episodes (self-treated hypoglycaemic episodes were classified as minor, while those requiring third-party assistance were considered major and the remainder as symptoms-only), incidence of adverse events, vital signs and clinical laboratory assessments.

*Statistical Analysis.* Efficacy endpoints were analysed using data from all subjects who received at least one dose of liraglutide or placebo [full analysis set (FAS); n = 264], and also on a subset of the FAS who completed more than 23 weeks of treatment and adhered to the study protocol and entry criteria [per protocol set (PPS)]. HBA1c and other efficacy endpoints were analysed using an ANOVA model with treatment group and pretrial SU as fixed effects and corresponding baseline values as a covariate. For the primary endpoint, if a test for comparison between 0.9 mg/day plus SU and placebo was significant, then the test of comparison between 0.6 mg/day plus SU and placebo was performed. For other efficacy endpoints, pairwise tests between liraglutide and placebo were performed if the overall test was significant. In addition, the comparison between liraglutide groups was performed on HBA1c and FPG (*post hoc* analysis).

## Results

### Patient Disposition and Demographics

Of the 308 subjects screened, 264 subjects were randomized and exposed to treatment and 241 completed the trial. Baseline characteristics were well balanced (table 1). Of the 23 subjects who withdrew from the study, the majority (10) withdrew from the placebo group because of ineffective therapy.

### Clinical Efficacy

*Glycated haemoglobin.* Once-daily treatment with liraglutide 0.6 and 0.9 mg significantly reduced and sustained HBA1c levels compared with placebo. The mean change in HBA1c from baseline to week 24 (LOCF) was greater with the higher liraglutide dose [0.9 mg, −1.56 (s.d. 0.84)] than with the other treatment groups [liraglutide 0.6 mg, −1.46 (s.d. 0.95), placebo −0.40 (s.d. 0.93); table 2, figure 2). Estimated HBA1c values at 24 weeks were significantly lower for liraglutide than for placebo (7.02 and 6.75% for 0.6 and 0.9 mg/day respectively, vs. 8.02%; $p < 0.0001$) with the treatment differences of −1.00% (95% CI −1.24, −0.75) for 0.6 mg/day liraglutide vs. placebo and −1.27% (95% CI −1.51, −1.02) for 0.9 mg/day liraglutide vs. placebo (table 2). A significantly greater percentage of subjects in liraglutide groups achieved HBA1c values of <7.0% (*post hoc* analysis) and <6.5% than subjects in the placebo group (figure 2).

*FPG and PPG.* Other glycaemic control parameters also showed significant improvement with liraglutide treatment. Full impact on FPG levels was achieved already at first visit at 4 weeks and levels were significantly lower in the two liraglutide treatment groups at week 24 compared with placebo (table 2, figure 3). Estimated means (s.e.) of FPG at LOCF in the FAS 0.6 and 0.9 mg/day liraglutide treatment groups were significantly lower compared with placebo: 7.34 mmol/l (0.19), 7.01 mmol/l (0.19) and 8.81 mmol/l (0.19) respectively ($p < 0.0001$). Glucose levels after a standard breakfast also showed significant dose–response in glucose [area under the curve $(AUC)_{(0-3h)}$] at LOCF (table 2). The estimated means of postprandial plasma glucose (post-PPG) at week 24 at all time points (30 min and 1–3 h after breakfast) for the two liraglutide treatment groups were lower than in the placebo

**Table 1.** Mean baseline patient demographics and disease characteristics

| | Liraglutide 0.6 mg OD | Liraglutide 0.9 mg OD | Placebo | Total/total mean |
|---|---|---|---|---|
| Number in FAS | 88 | 88 | 88 | |
| Number in PPS | 79 | 83 | 73 | |
| Number completing 24-week treatment (%) | 83 (94.3) | 84 (95.5) | 74 (84.1) | |
| Male : female, % | 60:40 | 67:33 | 65:35 | 64:36 |
| Age, years, % (s.d.) | 59.1 (10.3) | 61.3 (11.0) | 58.6 (9.7) | 59.7 (10.4) |
| Duration of diabetes, years, % (s.d.) | 9.3 (5.8) | 11.6 (7.7) | 10.1 (7.3) | 10.3 (7.0) |
| HBA1c, % (s.d.) | 8.60 (0.91) | 8.21 (0.78) | 8.45 (0.99) | 8.42 (0.91) |
| FPG, mmol/l (s.d.) | 9.85 (2.24) | 9.16 (2.07) | 9.48 (2.34) | 9.49 (2.23) |
| Body weight, kg (s.d.) | 66.1 (12.1) | 64.5 (12.0) | 66.7 (13.5) | 65.8 (12.5) |
| Waist circumference, cm (s.d.) | 88.0 (8.8) | 86.4 (9.2) | 88.1 (10.2) | 87.5 (9.4) |
| BMI, $kg/m^2$ (s.d.) | 25.3 (3.6) | 24.4 (3.4) | 24.9 (4.0) | 24.9 (3.7) |

BMI, body mass index; FAS, full analysis set; FPG, fasting plasma glucose; PPS, per protocol set; s.d., standard deviation.

**Table 2.** Effect of liraglutide on measures of glycaemia, body weight and cardiovascular events

| | | Liraglutide 0.6 mg/day | Liraglutide 0.9 mg/day | Placebo | p value pairwise comparison: both liraglutide doses vs. placebo |
|---|---|---|---|---|---|
| HBA1c (%) | Baseline, mean (s.d.) | 8.60 (0.92) | 8.23 (0.78) | 8.45 (0.99) | $p < 0.0001$ (both doses) |
| | Week 24 (LOCF), mean (s.d.) | 7.14 (0.89) | 6.67 (0.83) | 8.06 (1.13) | |
| | Liraglutide – placebo, mean (95% CI) | −1.00 (−1.24, −0.75) | −1.27 (−1.51, −1.02) | — | |
| Mean change in HBA1c – baseline to week 24 (%) | Week 24 (LOCF), mean (s.d.) | −1.46 (0.95) | −1.56 (0.84) | −0.40 (0.93) | N/A |
| Mean 7-point SMPG profile (mmol/l) | Baseline, mean (s.d.) | 11.75 (2.43) | 11.05 (2.42) | 10.91 (2.33) | $p < 0.0001$ (both doses) |
| | Week 24 (LOCF), mean (s.d.) | 9.09 (2.09) | 8.16 (2.07) | 10.56 (2.59) | |
| | Liraglutide – placebo, mean (95% CI) | −1.91 (−2.50, −1.31) | −2.47 (−3.06, −1.88) | — | |
| FPG (mmol/l) | Baseline, mean (s.d.) | 9.86 (2.26) | 9.18 (2.07) | 9.48 (2.36) | $p < 0.0001$ (both doses) |
| | Week 24 (LOCF), mean (s.d.) | 7.56 (1.61) | 6.90 (1.41) | 8.84 (2.41) | |
| | Liraglutide – placebo, mean (95% CI) | −1.47 (−1.92, −1.01) | −1.80 (−2.25, −1.34) | — | |
| $AUC_{(0-3h)}$ plasma glucose (mmol/l*h) | Baseline, mean (s.d.) | 44.27 (7.93) | 41.73 (8.29) | 41.77 (9.20) | $p < 0.0001$ (both doses) |
| | Week 24 (LOCF), mean (s.d.) | 35.07 (7.51) | 31.46 (7.14) | 39.84 (9.68) | |
| | Liraglutide – placebo, mean (95% CI) | −6.18 (−8.20, −4.15) | −8.35 (−10.35, −6.34) | — | |
| Body weight (kg) | Baseline, mean (s.d.) | 66.06 (12.19) | 64.57 (12.03) | 66.65 (13.49) | $p < 0.0001$ (0.6 mg/day + SU) |
| | Week 24 (LOCF), mean (s.d.) | 66.12 (12.34) | 64.20 (12.17) | 65.53 (13.68) | $p = 0.0071$ (0.9 mg/day + SU) |
| | Liraglutide – placebo, mean (95% CI) | 1.18 (0.63, 1.73) | 0.75 (0.21, 1.30) | — | |
| BNP (pg/ml) | Baseline, mean (s.d.) | 20.71 (27.37) | 19.03 (30.25) | 17.85 (24.63) | $p = 0.0018$ (0.6 mg/day + SU) |
| | Week 24 (LOCF), mean (s.d.) | 14.67 (21.99) | 15.13 (30.27) | 20.47 (28.90) | $p = 0.0157$ (0.9 mg/day + SU) |
| | Liraglutide – placebo, mean (95% CI) | −8.11 (−13.16, −3.06) | −6.24 (−11.28, −1.19) | — | |
| hsCRP (mg/dl) | Baseline, mean (s.d.) | 0.1326 (0.1447) | 0.0963 (0.1150) | 0.1478 (0.1523) | $p = 0.0218$ (0.6 mg/day + SU) |
| | Week 24 (LOCF), mean (s.d.) | 0.0823 (0.0867) | 0.0968 (0.1169) | 0.1225 (0.1303) | $p = 0.8143$ (0.9 mg/day + SU) |
| | Liraglutide – placebo, mean (95% CI) | −0.0338 (−0.0626, −0.0050) | −0.0035 (−0.0326, 0.0256) | — | |
| PAI-1 (ng/ml) | Baseline, mean (s.d.) | 36.26 (20.60) | 32.89 (23.22) | 34.69 (20.59) | Pairwise comparison N/A |
| | Week 24 (LOCF), mean (s.d.) | 34.31 (20.26) | 32.95 (21.77) | 32.79 (21.57) | $p = 0.9139$ for overall comparison |
| | Liraglutide – placebo, mean (95% CI) | 0.77 (−4.51, 6.06) | 1.11 (−4.18, 6.40) | — | |

AUC, area under the curve; BNP, brain natriuretic peptide; FPG, fasting plasma glucose; hsCRP, high-sensitivity C-reactive protein; N/A, not available; s.d., standard deviation; SMPG, self-monitored plasma glucose; SU, sulphonylurea.

group, with much lower mean values occurring in the liraglutide 0.9 mg group. The means of $AUC_{(0-3h)}$ at week 24 were also significantly lower in the two liraglutide groups vs. the placebo group ($p < 0.0001$).

Improvement in metabolic control was apparent in the self-monitored 7-point plasma glucose profiles at week 24 (figure 4), with significant reductions in mean glucose levels. Mean plasma glucose at LOCF was significantly lower in both of the liraglutide treatment groups than in the placebo group ($p < 0.0001$; table 2).

*Body Weight.* Mean body weight did not change from baseline in the two liraglutide treatment groups (0.6 mg/day, 0.06 kg; 0.9 mg/day, −0.37 kg) despite the improvements seen in glycaemic control. Weight decreased in the placebo group (−1.12 kg; table 2).

*Lipid Profile and Biomarkers for Cardiovascular Events.* No significant treatment effects were seen in any of the parameters of the lipid profile. The cardiovascular biomarker brain natriuretic peptide (BNP) was significantly lower in the two liraglutide groups compared with placebo (0.6 mg/day vs.

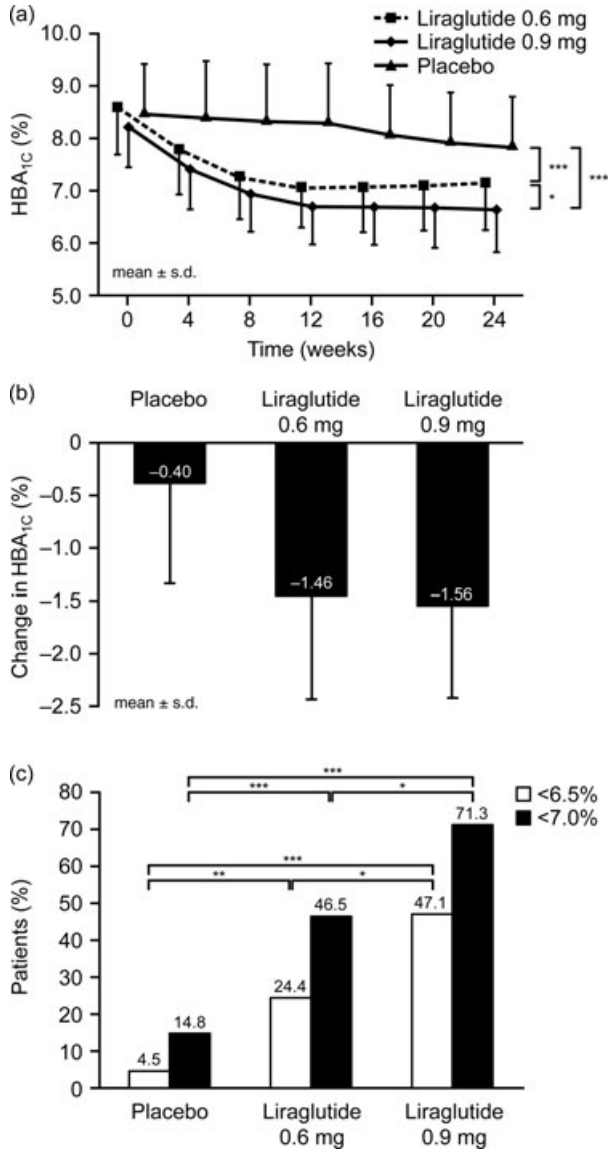


**Figure 2.** HBA1c (a) over time, (b) mean change from baseline and (c) percentage of subjects achieving HBA1c <7.0% and <6.5% after 24 weeks' treatment. *p < 0.05, **p = 0.0001, ***p < 0.0001. p value for (a) based on the ANOVA model of HBA1c at week 24 (LOCF), with baseline as a covariate and treatment group and pretrial SU treatment as fixed effects. The comparison between liraglutide groups was *post hoc* analysis.

placebo: p = 0.0018; 0.9 mg/day vs. placebo: p = 0.0157). Similarly, high-sensitivity C-reactive protein (hsCRP) was significantly lower in the 0.6 mg/day liraglutide group than in the placebo group (p = 0.0218), but no difference was seen between the 0.9 mg/day liraglutide vs. placebo groups (p = 0.8143). No significant treatment effect was seen in the estimated mean of PAI-1 at LOCF (week 24).

## Safety

A similar number of treatment-emergent adverse events were reported in all treatment groups: 0.6 mg/day (n = 67; 76.1%); 0.9 mg/day (n = 69; 78.4%) and placebo (n = 66; 75%). The

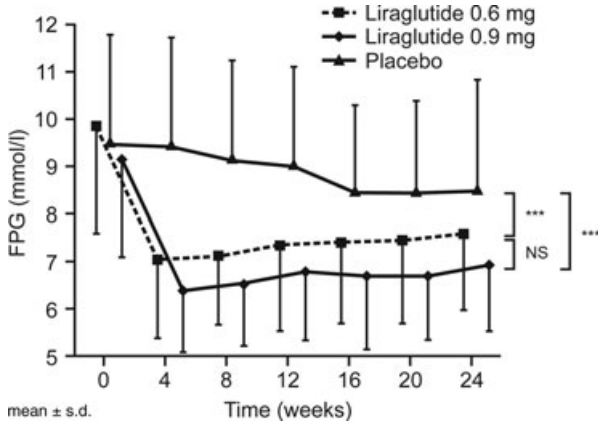


**Figure 3.** Fasting plasma glucose during 24 weeks' treatment. ***p < 0.0001. NS, non-significant. p values based on the ANOVA model of FPG at week 24 (LOCF) with baseline as a covariate and treatment group and pretrial SU treatment as fixed effects. The comparison between liraglutide groups was *post hoc* analysis.

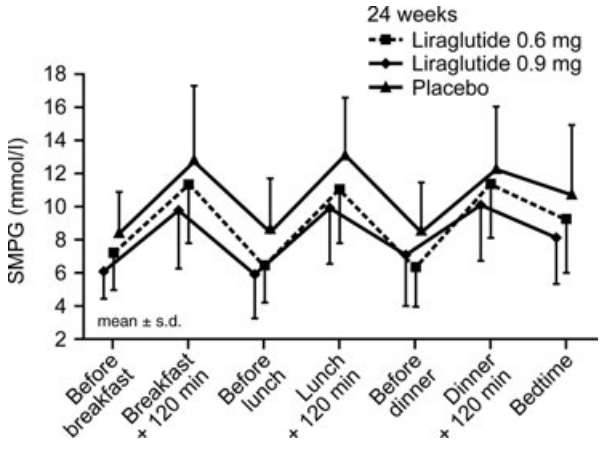


**Figure 4.** The 7-point plasma glucose profiles at baseline and 24 weeks for liraglutide 0.6 mg, liraglutide 0.9 mg and placebo.

most common adverse events were nasopharyngitis, diarrhoea and constipation. More subjects in the two liraglutide groups reported gastrointestinal adverse events during the first 4 weeks of the trial than subjects on placebo, but there were no major differences in gastrointestinal adverse events across groups overall.

A total of seven subjects withdrew from the study because of adverse events: three from the 0.6 mg/day group, two from the 0.9 mg/day group and two from the placebo group. No major hypoglycaemic episodes occurred in any of the treatment groups; however, the rate of minor confirmed hypoglycaemic episodes (events/patient/year) was higher in the 0.6 (2.17) and 0.9 mg/day (1.96) liraglutide groups than in the placebo group (1.01). Eight subjects reported eight treatment-emergent serious adverse events: three subjects in the 0.6 mg/day liraglutide group, two in the 0.9 mg/day group and three in the placebo group. No deaths were reported during the trial.

Plasma concentrations of calcitonin decreased in all groups, and there were no reports of pancreatitis. Diastolic and systolic blood pressure did not change in any of the treatment groups during the treatment period. Pulse increases above baseline were observed in the liraglutide groups (+3.4 beats/min in the 0.6 mg/day group and +3.7 beats/min in the 0.9 mg/day group), but were not considered clinically relevant.

## Discussion

The data presented in this study show that, as add-on to SU monotherapy, treatment with liraglutide provides superior glycaemic control (as measured by HBA1c levels) compared with placebo—with a difference between the highest liraglutide dose and placebo of 1.27%. The HBA1c effect was maintained throughout the 24 weeks (see figure 2). Similar improvements were observed for FPG and PPG, highlighting improved 24-h glycaemic control with OD liraglutide, with substantially more subjects reaching guideline-recommended glycaemic targets (particularly with liraglutide 0.9 mg/day).

In many cases, insulin treatment may provide similar decreases in HBA1c levels as seen in this study but not without the attendant weight gain seen in several studies [27–29]. In contrast, the Liraglutide Effect and Action in Diabetes (LEAD) programme of phase 3 trials has showed significant and clinically meaningful weight reductions with liraglutide across the continuum of care in Caucasian subjects with T2DM. In the current study, a relatively modest weight-lowering effect was observed in Japanese subjects receiving liraglutide, vs. the significant weight gain demonstrated by Caucasian subjects on SU monotherapy in the study by Marre et al. [16]. Overall, subjects in the liraglutide groups maintained stable body weight despite vast improvement in glycaemic control.

The modest weight response in this trial may be explained by the tendency of the Japanese population to typically have lower BMIs than their Caucasian counterparts [10,11]. This physiological difference was highlighted by the A Diabetes Outcome Progression Trial (ADOPT) in which Asians were found to have lower baseline BMI and weight circumference values compared to North American and European Caucasians [11]. According to the Japanese Society for the Study of Obesity (JSSO), a 'normal' BMI in Japan is between 18.5 and 25 kg/m$^2$ [30]. In the current study, mean baseline BMI for subjects in all three treatments groups ranged from 24 to 25 kg/m$^2$, and would therefore be considered within the normal range according to JSSO guidelines. The LEAD trials have shown that weight reduction is associated with baseline BMI: subjects with higher BMIs lose the most weight, while subjects with lower BMIs tend to lose the least [30]. This finding is supported by the results from the current study, in which Japanese subjects already within the normal BMI range at baseline maintained their weight throughout the study period. In contrast, subjects within the normal BMI range who were randomized to SU monotherapy showed significant weight loss. Consequently, a modest weight response to liraglutide is reassuring to subjects of normal BMI, in whom significant weight loss would be an adverse effect.

Although higher rates of hypoglycaemia were reported among subjects in the two liraglutide groups compared with those on placebo, the rate difference between the two liraglutide groups was minimal, and it should be borne in mind that glycaemic control levels were significantly lower in the liraglutide treated groups, making subjects more susceptible to SU-induced hypoglycaemia. The higher incidence of hypoglycaemic episodes occurred primarily during the first part of the trial, after which some subjects in the liraglutide treatment groups decreased the SU dose, and the incidence of hypoglycaemic episodes also decreased. In routine clinical care, it is suggested that any increase in hypoglycaemia be dealt with by decreasing the SU dose. When liraglutide is used without SU, incidence of hypoglycaemia is at the level of placebo [17].

The lack of reports of nausea in this study contrasts with results from a similar study in Caucasian subjects in which nausea was the most commonly reported adverse event [16]. In summary, these results confirm findings from previous studies of liraglutide in combination with an SU in both Japanese and Caucasian subjects with T2DM [28,31–34].

This study may have been limited by the relatively low numbers of subjects in each treatment arm; however, the 24-week study length provides ample time to monitor results of these treatments. The 28-week follow-up study that these subjects continued in will provide long-term safety and efficacy data on treatment with liraglutide combined with SU therapy vs. SU monotherapy.

In Japanese subjects with T2DM, OD liraglutide administered at 0.9 mg/day is both effective and well-tolerated in combination with SU agents, showing significantly greater glycaemic control than SU monotherapy, without causing adverse weight gain or loss.

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