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

Yutaka Seino^{1*}, Mads Frederik Rasmussen², Tomoyuki Nishida³, Kohei Kaku⁴

ABSTRACT

Aims/Introduction: Sulfonylurea (SU) agents are the most effective drugs at lowering blood glucose when used alone. However, their effectiveness declines after a certain period. The addition of liraglutide to existing SU therapy might reverse some of the known drawbacks of SU.

Materials and Methods: This multicenter, randomized, 52-week study assessed the long-term efficacy and safety of adding liraglutide at 0.6 or 0.9 mg/day to existing SU therapy in Japanese patients with inadequately controlled type 2 diabetes.

Results: In total, 264 patients were enrolled and received treatment. At week 52, HbA_{1c} in the liraglutide 0.6 mg, liraglutide 0.9 mg and placebo groups was reduced from 9.00 to 7.91%, from 8.61 to 7.33%, and from 8.85 to 8.79%, respectively. The mean difference of HbA_{1c} (95% CI) in the liraglutide 0.6 and 0.9 mg groups vs the placebo group was 0.96 (−1.25 to −0.67) and −1.33 (−1.62 to −1.04), respectively. For the liraglutide 0.6 mg, 0.9 mg and placebo groups, the Japanese Diabetes Society target HbA_{1c} of <6.9% was achieved by 15.1, 39.1 and 4.5% of patients, respectively. Mean fasting plasma glucose at week 52 was lower in the liraglutide groups compared with the placebo group, and mean bodyweight remained unchanged in the liraglutide groups. Most subjects in all three treatment groups reported mild adverse events. No major hypoglycemic episode was reported.

Conclusions: Once-daily administration of liraglutide in combination with SU for 52 weeks provided favorable metabolic control, a safety profile and did not alter bodyweight. This trial was registered with ClinicalTrials.gov (no. NCT00395746). (*J Diabetes Invest*, doi: 10.1111/j.2040-1124.2011.00103.x, 2011)

KEY WORDS: Glucagon-like peptide-1 receptor agonist, Liraglutide, Sulfonylurea

INTRODUCTION

The number of people with diabetes in Japan is approximately 8.9 million; adding those with impaired glucose tolerance brings the estimated total population with prediabetes and overt disease to 22.1 million¹. In Japan, type 2 diabetes accounts for 95% of the diabetic population. Patients with type 2 diabetes often present with increased glucagon secretion, postprandial hyperglycemia and gluconeogenesis².

Oral anti-diabetic drugs (OAD) given alone or in combination therapy initially lower blood glucose, but after a few years, deterioration of glucose control and marked decline of β -cell function usually develop. Among OAD, sulfonylurea (SU) agents are thought to be the most effective drugs at lowering blood glucose when used alone. However, although SU agents act by stimulating insulin secretion, their effectiveness declines after a certain period – so-called secondary SU failure³. It has been suggested that SU might actually impair β -cell function after prolonged use^{4,5}. Therefore, to prevent patients from developing further complications and to delay their transition to insulin dependence, it is important to keep them responsive to SU agents for as long as possible.

Liraglutide, a glucagon-like peptide-1 (GLP-1) analog, acts by increasing insulin secretion and decreasing glucagon secretion,

¹Kansai Electric Power Hospital, Osaka, ³Novo Nordisk Pharma Ltd, Tokyo,

⁴Endocrine and Diabetes Division, Department of Medicine, Kawasaki Medical School, Okayama, Japan, and ²Medical and Science, GLP-1, Novo Nordisk A/S, Bagsvaerd, Denmark

*Corresponding author. Yutaka Seino Tel: +81-6-6458-5821 Fax: +81-6-6458-8758 E-mail address: seino.yutaka@e2.kepc.co.jp

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and is glucose dependent. It reduces appetite and food intake, potentially leading to weight loss, and might possibly exert β -cell rescue^{6–11}. Furthermore, it has been shown that intravenous injection of native GLP-1 in type 2 diabetic patients with secondary SU failure improves basal and postprandial insulin secretion¹². Because liraglutide exerts its mode of action similarly to native GLP-1 via GLP-1 receptors located on islet β -cells, this agent might also cause these cells to undergo proliferation while preventing apoptosis to increase β -cell mass – as shown in experimental models^{13–15}.

The addition of liraglutide to existing SU therapy might reverse some of the known drawbacks of SU by prolonging and activating β -cell responsiveness and preventing β -cell fatigue. This strategy might delay the need to increase SU dose or even allow dose reduction and postpone initiation of insulin therapy. Furthermore, because patients on SU often experience body-weight gain, liraglutide's potential effects on reducing this parameter might be an additional advantage.

This trial assessed the long-term (1-year) efficacy and safety of adding liraglutide to existing SU plus diet therapy in patients with type 2 diabetes. The trial was carried out between November 2006 and April 2008. The results were included in the new drug application for liraglutide that was submitted to the Japanese Ministry of Health, Labour and Welfare (MHLW) in 2008. Liraglutide was approved by the MHLW for use in Japan in 2010.

MATERIALS AND METHODS

Patients

This trial was carried out in patients ≥ 20 years-of-age with inadequately controlled type 2 diabetes (HbA_{1c} 7.4–10.4%) previously on diet therapy and one SU agent, such as glibenclamide, gliclazide or glimepiride, for ≥ 8 weeks before entering the study.

Patients with proliferative retinopathy or maculopathy requiring acute treatment, impaired hepatic/renal function, serious heart disease, cancer, uncontrolled hypertension, suspected allergy to investigational products, pregnant and breast-feeding women, and patients previously receiving insulin therapy for more than 7 days within 12 weeks before commencement of the study were excluded.

The present study conforms to the principles of the Declaration of Helsinki and was approved by the institutional review board (IRB) at each site. Informed consent was obtained from all subjects before they undertook any trial-related activities.

Study Design

This trial comprised two parts: a 24-week double-blind portion designed to investigate the safety and efficacy of liraglutide, followed by a 28-week open-label observation period that assessed the safety and efficacy of this agent over the longer term (52 weeks). The results obtained during the first part of the study have been reported elsewhere¹⁶; this paper covers the data obtained after 52 weeks of treatment. We investigated the safety and efficacy of once-daily administration of liraglutide

0.6–0.9 mg/day for 52 weeks in combination with SU compared with SU monotherapy at lowering HbA_{1c} in Japanese patients with type 2 diabetes. We also examined the effects of the test regimens on glycemic control generally, and glucose metabolism-related parameters including bodyweight and markers of β -cell function. Safety assessment encompassing investigation of adverse events (AE) and hypoglycemic episodes associated with taking the test regimens was also carried out. AE were classified as major (hypoglycemia requiring third-party assistance), minor (self-treated hypoglycemia) or symptoms only (remainder of cases). Standard safety parameters were clinical laboratory assessments including calcium and calcitonin, vital signs, electrocardiogram, funduscopy/fundusphotography and liraglutide antibodies.

This was a multicenter, randomized, 52-week study carried out in diabetic patients who were previously undergoing treatment with a SU agent. Subjects were randomly allocated into liraglutide 0.6 mg/day, liraglutide 0.9 mg/day or placebo groups; treatments were subcutaneously given once daily in the morning or evening. Existing SU agents were given in accordance with the daily dosing instructions on the package insert (in Japan: glibenclamide 1.25–10 mg; gliclazide 40–160 mg; glimepiride 1–6 mg) and continued as a rule without change of dosage throughout the study period – although the dosage of SU could be reduced as necessary in the case of hypoglycemia or other symptoms arising, at the investigators' discretion. Safety and efficacy of the test regimens were assessed at the end of the 52-week treatment period. To reduce the possibility of gastrointestinal (GI) AE, subjects assigned to active treatment groups first entered a 2-week dose-escalation period, which has been shown to be effective in a phase I clinical investigation¹⁷, followed by a 50-week dose maintenance period. During this trial, patients were prohibited from taking other OAD, insulin preparations and systemic corticosteroids.

HbA_{1c} was assessed by high-performance liquid chromatography (HPLC) every 4 weeks. HbA_{1c} (%) values were estimated as the National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) using the formula: HbA_{1c} (%) = HbA_{1c} (Japan Diabetes Society [JDS]; %) + 0.4%, considering the relational expression of HbA_{1c} (JDS) measured by the previous Japanese standard substance and measurement methods and HbA_{1c} (NGSP)¹⁸. A 7-point plasma glucose (PG) profile (before and 120 min after breakfast, lunch and dinner, and at bedtime) was measured by self-monitoring at home using an automated glucose meter at baseline and every 3 months until the end of the study.

Fasting insulin, proinsulin, C-peptide and glucagon were assessed at baseline, week 24 and the end of the study. Homeostasis model assessment-B (HOMA-B) was calculated by the following formula:

$$\text{HOMA-B} = 360 \times \text{fasting insulin } (\mu\text{U/mL}) / (\text{fasting PG} [\text{mg/dL}] - 63).$$

Statistical Analysis

For each efficacy end-point after the 52-week treatment, a 95% confidence interval (95% CI) for the mean difference (each liraglutide – placebo) was calculated by analysis of variance (ANOVA) model with treatment group and pre-trial SU as fixed effects and corresponding baseline value as covariate. The last observation carried forward (LOCF) approach was used for subjects who had at least one valid post-baseline measurement. Furthermore, each end-point was summarized using summary statistics by visit and treatment group.

RESULTS

Among the 308 patients initially screened, 267 were randomized and 264 received study treatments. The proportions of patients in the placebo, liraglutide 0.6 and 0.9 mg groups who completed the 52-week study were 75.0, 88.6 and 95.5%, respectively. Most patients who withdrew did so as a result of ineffective therapy in the placebo group. However, no patient in the liraglutide 0.9 mg + SU group dropped out for this reason.

Baseline, clinical and demographic data of the subjects are shown in Table 1. Overall, background data were comparable across the three treatment groups; however, at baseline, subjects in the liraglutide 0.9 mg + SU group had slightly lower HbA_{1c} and longer duration of diabetes compared with the other two treatment groups.

At week 52 vs baseline, HbA_{1c} in the liraglutide 0.6 mg, liraglutide 0.9 mg and placebo groups reduced from 9.00 to 7.91%, from 8.61 to 7.33% and from 8.85 to 8.79%, respectively. The mean difference of HbA_{1c} (95% CI) in the liraglutide 0.6 and 0.9 mg groups vs the placebo group was –0.96 (–1.25 to –0.67) and –1.33 (–1.62 to –1.04), respectively (Table 2).

Mean HbA_{1c} values in the three treatment groups throughout the trial are shown in Figure 1. In the liraglutide 0.9 mg + SU group, mean HbA_{1c} gradually reduced from baseline to week 12 and was maintained thereafter, whereas mean HbA_{1c} in the liraglutide 0.6 mg + SU group initially followed the same pattern to week 12, but increased thereafter. In contrast, HbA_{1c} in the placebo group decreased slightly from baseline to week 32 and increased thereafter. At week 52, mean HbA_{1c} was lowest in the liraglutide 0.9 mg group, followed by that in the liraglutide 0.6 mg group.

At week 52, the JDS target HbA_{1c} of <6.9% was achieved by 15.1% of patients in the liraglutide 0.6 mg group and 39.1% of those in the liraglutide 0.9 mg group; whereas in the placebo group, the proportion achieving this target was only 4.5%.

Mean fasting PG at week 52 was lower in the two liraglutide groups than in the placebo group based on 95% CI for the treatment differences (Table 2). PG values at each point in the 7-point PG profile for the two liraglutide groups were lower than baseline values starting from week 12 until the end of the study. Mean PG (the mean of the 7-point PG profile) and the mean postprandial PG increment (the mean value of PG after meals) at week 52 were lower than those observed in the placebo group based on the 95% CI for the treatment differences (Table 2).

Mean bodyweight remained essentially unchanged in the two liraglutide groups, whereas a slight reduction of 1.1 kg was noted in the placebo group.

At week 52 vs baseline, mean HOMA-B was higher and mean proinsulin/insulin and proinsulin/C-peptide ratios were lower in the two liraglutide groups than in the placebo group (data not shown).

Table 1 | Baseline demographic characteristics of subjects

Category	0.6 mg + SU	0.9 mg + SU	Placebo + SU	Total
No. subjects	88	88	88	264
Sex, <i>n</i> (%)				
Male	53 (60.2)	59 (67.0)	57 (64.8)	169 (64.0)
Female	35 (39.8)	29 (33.0)	31 (35.2)	95 (36.0)
Age (years)	59.1 ± 10.3	61.3 ± 11.0	58.6 ± 9.7	59.7 ± 10.4
Bodyweight (kg)	66.2 ± 12.0	64.5 ± 12.0	66.8 ± 13.7	65.8 ± 12.6
BMI (kg/m ²)	25.3 ± 3.6	24.4 ± 3.8	24.9 ± 4.0	24.9 ± 3.7
Waist circumference (cm)	88.0 ± 8.8	86.4 ± 9.2	88.1 ± 10.2	87.5 ± 9.4
HbA _{1c} (%)	9.00 ± 0.91	8.61 ± 0.78	8.85 ± 0.99	8.82 ± 0.91
Duration of diabetes (years)	9.3 ± 5.8	11.6 ± 7.7	10.1 ± 7.3	10.3 ± 7.0
Pre-trial SU treatment, <i>n</i> (%)				
Glibenclamide	20 (22.7)	21 (23.9)	20 (22.7)	61 (23.1)
Dose (mg)	4.5	6.1	5.2	5.3
Gliclazide	7 (8.0)	6 (6.8)	6 (6.8)	19 (7.2)
Dose (mg)	68.6	66.7	53.3	63.2
Glimepiride	61 (69.3)	61 (69.3)	62 (70.5)	184 (69.7)
Dose (mg)	3.1	3.0	3.0	3.0
Concomitant illness, <i>n</i> (%)				
Yes	86 (97.7)	87 (98.9)	88 (100.0)	261 (98.9)
No	2 (2.3)	1 (1.1)	0 (0.0)	3 (1.1)

Mean ± SD. BMI, body mass index; SU, sulfonylurea.

Table 2 | Analysis of variance of HbA_{1c}, fasting plasma glucose, mean plasma glucose and mean postprandial plasma glucose increment at week 52

Parameter	<i>n</i>	Mean (SE)	Treatment difference (95% CI)†
HbA _{1c} (%)			
Liraglutide 0.6 mg + SU	86	7.8 (0.1)	−0.96 (−1.25 to −0.67)
Liraglutide 0.9 mg + SU	87	7.5 (0.1)	−1.33 (−1.62 to −1.04)
Placebo + SU	88	8.8 (0.1)	
Fasting PG (mg/dL)			
Liraglutide 0.6 mg + SU	85	140.3 (4.0)	−24.4 (−33.8 to −14.9)
Liraglutide 0.9 mg + SU	86	134.5 (4.1)	−30.2 (−39.6 to −20.7)
Placebo + SU	87	164.6 (4.0)	
Mean PG (mg/dL)			
Liraglutide 0.6 mg + SU	81	171.4 (5.1)	−34.5 (−46.8 to −22.2)
Liraglutide 0.9 mg + SU	80	159.6 (5.3)	−46.3 (−58.5 to −34.2)
Placebo + SU	82	205.9 (4.8)	
Mean postprandial PG increment (mg/dL)			
Liraglutide 0.6 mg + SU	82	82.3 (4.8)	−7.1 (−18.4 to 4.2)
Liraglutide 0.9 mg + SU	80	76.1 (5.0)	−13.0 (−24.7 to −1.9)
Placebo + SU	85	89.4 (4.9)	

†Defined as (each liraglutide + SU) − (placebo + SU). SU, sulfonylurea.

Figure 1 | Time-course of HbA_{1c}.

Most subjects in all three treatment groups reported AE (liraglutide 0.6 mg group, 95.5%; liraglutide 0.9 mg group, 89.8%; placebo group 94.3%). The majority of treatment-emergent AE (TEAE) were mild in severity. The most common TEAE among the three groups was nasopharyngitis (occurring in 42.0, 43.2 and 39.8% of subjects, respectively). TEAE possibly or probably related to taking the trial products were reported in ≥5% of subjects and are summarized in Table 3.

No major hypoglycemic episode was reported. The rate of minor hypoglycemic episodes (events/patient/year) was 1.44 in the liraglutide 0.6 mg group, 1.37 in the liraglutide 0.9 mg group and 1.29 in the placebo group; the rate of symptoms-only hypoglycemic episodes was 1.69, 2.35 and 1.71, respectively. Change over time in the incidence of hypoglycemia is shown in

Table 3 | Treatment-emergent adverse events with a possible or probable relationship to trial products occurring in ≥5% of subjects

System organ class/preferred term	N (%) E		
	0.6 mg + SU	0.9 mg + SU	Placebo + SU
Subjects exposed (<i>n</i>)	88	88	88
All adverse events	34 (38.6) 75	31 (35.2) 68	34 (38.6) 57
GI disorders	18 (20.5) 21	21 (23.9) 34	15 (17.0) 22
Constipation	6 (6.8) 7	7 (8.0) 8	3 (3.4) 4
Diarrhea	4 (4.5) 4	6 (6.8) 8	6 (6.8) 6
Investigations	7 (8.0) 12	3 (3.4) 3	6 (6.8) 6
Alanine aminotransferase increased	5 (5.7) 6	1 (1.1) 1	1 (1.1) 1
General disorders/administrative site reactions	6 (6.8) 7	4 (4.5) 5	4 (4.5) 4
Skin/subcutaneous tissue disorders	7 (8.0) 8	3 (3.4) 5	3 (3.4) 4

E, total number of adverse events; N, number of subjects with adverse events.

Figure 2 | Time-course of hypoglycemic episodes. In the groups receiving liraglutide, the incidence of hypoglycemia was high during the first 4 weeks then decreased to a level similar to that seen in the placebo group throughout the remainder of the 52-week study.

Figure 2. In the groups receiving liraglutide, the incidence of hypoglycemia was higher than in the placebo group during the first 4 weeks, then decreased to a level similar to that seen in the placebo group throughout the remainder of the study.

GI disorders accounted for 48.9, 47.7 and 38.6% of subjects in the liraglutide 0.6 mg, liraglutide 0.9 mg and placebo treatment arms, respectively. Although more liraglutide + SU-treated subjects experienced GI disorders compared with those on SU alone during the first 4 weeks, the proportions of affected individuals were comparable among the groups thereafter. Pancreatitis did not occur in any subject during this trial. Nine patients withdrew from the study as a result of AE (liraglutide 0.6 mg group,

$n = 5$; liraglutide 0.9 mg group, $n = 2$; placebo group, $n = 2$). Twelve serious AE were reported in 12 subjects (liraglutide 0.6 mg group, $n = 4$; liraglutide 0.9 mg group, $n = 3$; placebo group, $n = 5$). No deaths occurred during the present study. No clinically relevant change in laboratory parameters was noted in any patients. No significant treatment effect was seen in calcitonin. Although 13 patients in the liraglutide 0.6 mg group and 14 in the liraglutide 0.9 mg group were positive for liraglutide antibodies at week 52, no relationship was detected between change in antibodies and that of HbA_{1c}. Furthermore, changes in HbA_{1c} in these patients were comparable with those in all patients treated with liraglutide.

DISCUSSION

The results of the present trial show that both test doses of liraglutide (0.6 and 0.9 mg), in combination with a SU agent, provided favorable glycemic control. HbA_{1c} was lower in the two liraglutide + SU groups compared with the group receiving SU + placebo. Liraglutide provided a sustained effect on HbA_{1c} over 52 weeks. Furthermore, liraglutide's effects were dose-dependent, with greater reductions observed in patients receiving 0.9 mg/day compared with those receiving 0.6 mg/day. The estimated treatment difference (liraglutide + SU – placebo) in HbA_{1c} at week 52 was -0.96% in the liraglutide 0.6 mg group and -1.33% in the liraglutide 0.9 mg group. Furthermore, the JDS target HbA_{1c} indicative of 'good glycemic control' (HbA_{1c} < 6.9%) was achieved by 15.1 and 39.1% of subjects in the two groups, respectively, compared with only 4.5% in the placebo group. Sustained effects of liraglutide in combination with SU were also noted on fasting PG, postprandial PG and 7-point PG profiles after 52 weeks of treatment.

To prevent the onset of complications that might occur as diabetes progresses and glycemic control gradually worsens, patients are typically first treated with diet and exercise, followed by monotherapy with an OAD, then combination OAD therapy and finally insulin therapy¹⁹. However, most diabetic individuals eventually show poor glycemic control. Furthermore, many existing pharmacological therapies are associated with side-effects including weight gain and hypoglycemia. The Liraglutide Effect and Action in Diabetes (LEAD) program of clinical trials^{20–23} showed that liraglutide alone or in combination with OAD is associated with equivalent or superior improvements in glycemic control, reduced risk of hypoglycemia and modest weight loss or weight neutrality, compared with alternative agents used in the treatment of diabetes, suggesting its potential as first- or second-line therapy.

Previous studies have found that liraglutide is useful as monotherapy, with better improvements of glycemic control parameters and more favorable impact on bodyweight compared with placebo and glimepiride alone^{6–8,23–25}. Furthermore, these effects were dose-dependent^{20–23}. In the LEAD-1 trial²⁰, treatment with liraglutide 0.6, 1.2 and 1.8 mg/day in combination with glimepiride led to better reduction of HbA_{1c} in patients with poorly controlled diabetes than rosiglitazone plus glimepiride at the

end of the 26-week observation period. Furthermore, whereas patients treated with liraglutide at the highest dose lost -0.2 kg in bodyweight, those in the rosiglitazone group showed substantial weight gain.

In the present study, we observed substantial reductions of HbA_{1c} by adding liraglutide to existing SU therapy in comparison with maintaining existing SU therapy in poorly controlled diabetic patients for 52 weeks. Furthermore, among patients given liraglutide at the higher dose, more than one-third achieved the JDS definition of good glycemic control. Therefore, the addition of liraglutide to SU therapy comprising glibenclamide, gliclazide or glimepiride in patients showing poor responses to these agents and elevated HbA_{1c} seems useful for reducing this parameter with durable effects.

Liraglutide given in combination with SU to subjects with type 2 diabetes was generally safe and well tolerated. The safety data obtained over 52 weeks raised no safety concerns. Most TEAE were mild in severity. As expected in a long-term clinical trial carried out in patients with type 2 diabetes, the majority of subjects experienced at least one TEAE.

GLP-1 and GLP-1 analogs are known to cause GI side-effects, such as nausea, diarrhea and vomiting, particularly when not initially titrated in a stepwise manner. In the present trial, the dose was increased at 1-week intervals, which has been reported to reduce the number of GI side effects¹⁷. Interestingly, the most frequently observed GI disorder arising in our patients who received liraglutide was not nausea/vomiting, but constipation. Although there were more GI-related TEAE reported by subjects in the two liraglutide groups compared with the placebo group, these occurred mainly in the first 4 weeks of the study and their incidence tended to even off among the three groups thereafter.

No major hypoglycemic episodes were reported in any treatment group. Mild episodes of hypoglycemia and hypoglycemic symptoms were observed at comparable rates in the three groups. It has been reported that because liraglutide lowers PG levels in a glucose-dependent manner, the incidence of hypoglycemia tends to be low in monotherapy^{6,23,25,26}. When coadministered with SU, however, hypoglycemia might appear and caution should be exercised. In such patients, SU dose reductions might be necessary to avoid hypoglycemia.

In the present study, the incidence of hypoglycemia in patients receiving liraglutide was high during the first 4 weeks then decreased to a level similar to that noted in the placebo group throughout the remainder of the treatment period. However, during the first 4 weeks, dose reduction of SU was carried out in 12.5–17.0% of patients in the liraglutide groups. In these patients, the mean glibenclamide dose decreased from 5.3 mg at baseline to 3.5 mg at week 52 in the liraglutide 0.6 mg group, and from 6.3 to 3.4 mg, respectively, in the liraglutide 0.9 mg group. The mean glimepiride dose decreased from 4.7 mg at baseline to 2.8 mg at week 52 in the liraglutide 0.6 mg group, and from 4.1 to 2.1 mg, respectively, in the liraglutide 0.9 mg group. No data are shown for gliclazide. Despite the reductions in SU dose in these patients, liraglutide elicited improvements in HbA_{1c} that

were comparable with those in patients who did not require SU dose reduction. These decreases in SU dose might have contributed to the decrease in the incidence of hypoglycemia. Indeed, hypoglycemia incidence during the period from weeks 24 to 52 was lower in the liraglutide plus SU groups than in the placebo plus SU group. As a result, overall incidence rates were comparable among the three treatment groups. Therefore, if liraglutide is prescribed to patients in addition to SU in clinical practice, it is recommended to consider measures such as SU dose reduction, taking into account the possible development of hypoglycemia in the early phase of combination therapy.

The majority of subjects had calcitonin values below the detection limit and no significant shift of this parameter was noted in any treatment group. Pancreatitis was not reported during the present study. When HbA_{1c} after 52 weeks was compared between subjects with and without liraglutide antibodies, no difference was seen between the antibody-positive group and the entire cohort receiving liraglutide, suggesting that the antibodies developed during this trial had no clinically significant impact on overall metabolic control.

GLP-1 and GLP-1 analogs have been shown in animal models to preserve or even improve β -cell function, an effect that makes these agents unique in the treatment of type 2 diabetes^{14,27–30}. In this regard, HOMA-B and proinsulin/insulin and proinsulin/C-peptide ratios all suggested a significant beneficial effect in subjects treated with liraglutide. However, the longer-term consequences of this observation require further investigation.

The effect of liraglutide on bodyweight in Japanese subjects with type 2 diabetes showed a somewhat different trend to that noted in non-Japanese trials, where greater reductions of ≤ 3.0 kg were observed^{6,8,23–25}. This might be an artifact of the lower baseline BMI in the present study; alternatively, genetic differences in the study populations could be an underlying factor. Nonetheless, no change in bodyweight was seen in the two liraglutide plus SU treatment groups in the present study. The only strategy that can lower HbA_{1c} in a similar manner as liraglutide is insulin treatment, and this is almost always followed by bodyweight increase. Although patients in the placebo group showed weight decrease, the difference in metabolic control, with a significantly higher HbA_{1c}, could contribute to this: it is well known that patients with poor glycemic control excrete glucose in the urine and this condition results in caloric loss.

The study population comprised patients with a mean duration of diabetes of 10.3 years. Accordingly, although the eligibility criteria stated that patients were to be using SU monotherapy in combination with diet therapy for ≥ 8 weeks before entering the study, it is possible that some patients had used other OAD at some stage in their diabetes treatment and some patients might have stopped other OAD shortly before the 8-week cut-off. Nevertheless, we excluded patients who were using other OAD or insulin within 8 weeks before starting the study. Therefore, any 'hangover' effects of other OAD/insulin should be minimal, and the results of the present study reflect the effects of adding liraglutide to SU.

It is also possible that the type and dose of SU used might have influenced the outcomes of this trial. However, such effects should be negligible, because the efficacy end-points were assessed using analysis of variance in which pretrial SU was included as a fixed effect to adjust for the type of SU used.

In conclusion, once-daily administration of liraglutide 0.6 and 0.9 mg in combination with a SU agent for 52 weeks provides favorable metabolic control and safety profile. At the end of this trial, HbA_{1c} was lower in the two liraglutide treatment groups than in the placebo group. Moreover, more patients on liraglutide plus SU achieved the JDS target for good glycemic control. No safety concerns were raised during 1-year treatment with the test regimens. No major hypoglycemic episodes were reported. The incidence of minor hypoglycemia was high in the groups receiving liraglutide during the first 4 weeks, but leveled off thereafter; overall, incidence rates were comparable among the three treatment groups, possibly a result of SU dose reduction early in the study. Although more patients in the two liraglutide groups than the placebo group reported GI-related TEAE, the difference was mainly observed during the first 4 weeks of the study. Although bodyweight was slightly higher in the two liraglutide groups compared with the placebo group at study end, this parameter nonetheless remained unchanged vs baseline.

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