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Dose-dependent improvement in glycemia with once-daily liraglutide without hypoglycemia or weight gain: A double-blind, randomized, controlled trial in Japanese patients with type 2 diabetes

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ABSTRACT

Aims: To evaluate dose response efficacy and safety of once daily human GLP 1 analog liraglutide in Japanese subjects with type 2 diabetes.

Methods: Patients (226, treated with diet with/without OADs, mean HbA_{1c} 8.30%, mean BMI 23.9 kg/m²) were randomized after OAD discontinuation and washout to receive liraglutide 0.1, 0.3, 0.6 or 0.9 mg once daily, or placebo in double blind, parallel group design for 14 weeks.

Results: Liraglutide dose levels reduced HbA_{1c} versus placebo (by 0.79%, 1.22%, 1.64% and 1.85%, respectively; $p < 0.0001$ for linear contrast). Liraglutide 0.9 mg/day resulted in 75% of patients achieving HbA_{1c} $< 7.0\%$ and 57% achieving HbA_{1c} $< 6.5\%$. There were no major or minor hypoglycemic events. Liraglutide also reduced, with significant dose response (each $p < 0.0001$ for linear contrast) versus placebo: fasting plasma glucose (up to 2.5 mmol/L), postprandial (0–3 h) glucose excursion (up to 12.8 mmol/L h); and increased postprandial insulin secretion (up to 23.0 $\mu\text{U}/(\text{mL h})$) and beta cell function as evaluated by HOMA β (up to around 20.0 ($\mu\text{U}/\text{mL})/(\text{mg}/\text{dL})$). Body weight was unchanged; no development of liraglutide antibodies was detected.

Conclusions: Liraglutide was highly effective and well tolerated at doses up to 0.9 mg/day in Japanese patients with type 2 diabetes, allowing glycemic control without weight gain or hypoglycemia.

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1. Introduction

Type 2 diabetes is a multifactorial disease, in which individuals, to a varying degree, exhibit failing beta cell function, weight gain and increasing insulin resistance over time. The relative

importance of these factors differs between individuals and between populations, and it is well established that the pathophysiology of type 2 diabetes differs between Japanese and Caucasian patients. Insulin secretory capacity in Japanese patients with type 2 diabetes has been shown to be half of that

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seen in Caucasian patients, a difference that is particularly pronounced for meal related secretion [1–3]. Japanese patients, in addition, typically have less insulin resistance compared to Caucasians and are generally less obese, with a typical body mass index (BMI) of 23–24 kg/m² [4]. However, deteriorating glycemic control is often observed resulting in increased risk of microvascular and macrovascular complications. Available treatments for type 2 diabetes are often associated with undesirable effects (such as weight gain, hypoglycemia or edema) that limit their acceptability and potential for reaching treatment targets. There remains an urgent need for new therapies that address the multiple dysfunctions in type 2 diabetes without limitations of poor tolerability or acceptability.

Glucagon like peptide 1 (GLP 1) is an incretin hormone with a broad spectrum of physiological actions. Analogs of GLP 1 may potentially be able to modulate the otherwise inevitable progression of type 2 diabetes [5–7]. Liraglutide is a long acting human GLP 1 analog that has a high degree of homology to native GLP 1 but, via acylation to myristic acid, achieves a longer plasma half life of 13 h and can thus be administered once daily [8–10].

Previous studies with liraglutide in Japanese subjects have included single dose and 21 day stepwise dose escalation (up to 15 µg/kg) studies in healthy subjects and a 14 day dose escalation study (to 10 µg/kg) in subjects with type 2 diabetes [11]. Studies in non Japanese subjects with type 2 diabetes have shown that liraglutide is able to achieve sustained improvements in glycemic control with significant reduction in body weight and with a very low risk of hypoglycemia [7,12–14]. Liraglutide has shown favorable effects on several parameters of beta cell function [10,15–17], and animals treated with liraglutide have shown increases in beta cell mass [18]. Recent data in non Japanese subjects with type 2 diabetes also suggest potentially beneficial effects of liraglutide on systolic blood pressure (SBP), triglycerides and cardiovascular biomarkers [19].

The present study was conducted to assess the efficacy, safety and optimal dose for liraglutide during sustained treatment in Japanese subjects with type 2 diabetes.

2. Subjects and methods

This was a multicenter, double blind, randomized, parallel group phase 2 trial to evaluate the dose response relationship on glycemic control of four doses of liraglutide and placebo in Japanese subjects with type 2 diabetes. The primary efficacy endpoint was HbA_{1c} after 14 weeks of treatment, with other measures of glycemic control (fasting plasma glucose (FPG), postprandial plasma glucose (PPG), self monitored plasma glucose profile) as secondary endpoints. The study was performed at 63 centers in Japan between March 2005 and May 2006. The study was performed in accordance with the Declaration of Helsinki, with informed consent of subjects and with approval of relevant ethics committees. Trial registration numbers were NCT00154414 and JapicCTI 050131.

Patients included were to have type 2 diabetes treated with diet therapy with or without oral antidiabetic drug (OAD) monotherapy, HbA_{1c} ≥7.0% and <10.0%, to be aged

between 20 and 75 years and to have BMI <30 kg/m². Patients treated with insulin or insulin sensitizer within 16 weeks, or receiving or expected to receive systemic corticosteroids, were excluded, as were those with impaired hepatic or renal function (serum glutamic oxaloacetic transaminase or serum glutamic pyruvic transaminase >80 IU/L, or serum creatinine ≥1.7 mg/dL), congestive heart failure (New York Heart Association class III or IV), unstable angina pectoris or myocardial infarction within 12 months, uncontrolled hypertension (SBP >160 mmHg or diastolic blood pressure >100 mmHg), non stabilised proliferative retinopathy or maculopathy.

The trial consisted of an 8 week run in period following screening (at which point OAD therapy, if any, was discontinued and during which an FPG <7.5 or ≥11.1 mmol/L at either of two visits was cause for exclusion), a 2 week dose titration period and a 12 week maintenance phase. Patients were randomized at the end of the run in period to liraglutide or placebo in four cohorts, each planned to contain 50 patients; in each cohort a planned 40 patients received one of four liraglutide doses (0.1 mg/day; 0.3 mg/day; 0.6 mg/day or 0.9 mg/day) and 10 received placebo. Liraglutide doses in the 0.6 and 0.9 mg/day cohorts were increased from a starting dose of 0.3–0.6 mg/day after 1 week and, in the 0.9 mg/day cohort, by a further 0.3 mg/day after 2 weeks. Randomization was stratified by pre treatment (with or without OAD monotherapy) and was performed by sealed code by a central telephone registration centre; allocation to liraglutide or placebo in each cohort was blinded to subject and investigator. Dynamic allocation was employed in order to guarantee a balanced allocation within strata of pre trial treatment. Liraglutide was supplied by Novo Nordisk A/S (Copenhagen, Denmark) as a 6.25 mg/mL solution, and visually indistinguishable liraglutide vehicle as placebo. Trial medication was administered by abdominal subcutaneous injection using pre filled pen and needle set (FlexPen[®], PenNeedle[®], Novo Nordisk), once daily in the evening (at the same time every day for each subject, as far as possible).

HbA_{1c} and FPG were measured at baseline, after 2, 6 and 10 weeks and at the end of the trial. A meal test, using a standard Japanese style breakfast, was performed at baseline and at the end of the trial; plasma glucose, insulin and glucagon being measured and the pre breakfast plasma glucose being taken as measure of FPG. Fasting pro insulin and C peptide levels were also recorded. All analyses were carried out by a central laboratory (Mitsubishi Kagaku IRI, Inc., Tokyo, Japan), except for a seven point plasma glucose profile which was measured before and approximately 2 h after each meal, and at bedtime by self monitoring at home using glucose meters (Glutest Ace[®], Glutest PRO[®], Sanwa Kagaku, Nagoya, Japan; Glucocard Diameter or Glucocard Diameter α, Arkray KDK Corp., Kyoto, Japan) before start of treatment and end of study, furthermore plasma liraglutide concentrations were measured using ELISA by Capio Diagnostics (Copenhagen, Denmark), and liraglutide antibodies were measured by radioimmunoassay by Novo Nordisk A/S Immunochemistry (Måløv, Denmark). Safety assessments included thyroid ultrasonography at screening and end of study, electrocardiography and clinical laboratory assessments including calcitonin. Beta cell function and insulin resistance were assessed from fasting insulin and plasma glucose values

using the homeostasis model assessment (HOMA) β and HOMA R models, respectively [20]:

$$\text{HOMA } \beta = 360 \times \text{fasting insulin} / (\text{FPG} - 63)$$

$$\text{HOMA R} = (\text{fasting insulin} \times \text{FPG}) / 405$$

where units of insulin and glucose $\mu\text{U/mL}$ and mg/dL , respectively.

Efficacy endpoints were analyzed using data from all patients who received trial product and for whom any efficacy data were recorded. Safety endpoints were recorded for any patient receiving any dose of trial product. HbA_{1c} and other efficacy endpoints were analyzed using an ANOVA model with dose group and pre trial treatment (with and without OAD) as fixed effects and value at baseline as covariate. The existence of a monotonic dose response relationship was assessed for each endpoint using an F test for linear contrast with contrast coefficient of (2, -1, 0, 1, 2). A sequentially rejecting Dunnett test was used to perform pairwise comparison of HbA_{1c} levels in liraglutide groups versus placebo. Required sample size was calculated as 32 per dose group, based on a two sided 5% significance level for the F test for linear contrast in the primary endpoint with 80% power. Randomization of a minimum of 200 subjects was planned, allowing for an expected dropout rate of 15%.

3. Results

A total of 372 patients were screened, of whom 226 were randomized to study cohorts and exposed to treatment

(Table 1). Mean HbA_{1c} was 8.30%; baseline characteristics were comparable across study groups (Table 1). Sixteen patients withdrew from the study, the largest number from the groups allocated to placebo (eight withdrawals).

Mean HbA_{1c} was reduced by all liraglutide dose levels relative to placebo (Fig. 1), the magnitude of the treatment effect ranging from 0.79 percentage points in the 0.1 mg/day group to 1.85 percentage points with 0.9 mg/day liraglutide (Table 2). HbA_{1c} levels below 7.0% were achieved by 22%, 43%, 62% and 75% of patients receiving liraglutide, 0.1, 0.3, 0.6 and 0.9 mg/day, respectively, and 9% of those receiving placebo. The proportion of patients achieving HbA_{1c} <6.5% ranged from 7% to 57% in the liraglutide dose groups, and 2% in the placebo group (Table 2). A monotonic dose response relationship was confirmed in HbA_{1c} level, with $p < 0.0001$ for linear contrast. Pairwise comparison showed statistically significant differences in HbA_{1c} levels versus placebo in all liraglutide groups at 14 weeks.

Self monitored seven point plasma glucose profiles showed reductions in mean glucose levels across the day; mean AUC values for glucose across the seven point profiles were lower than placebo with all liraglutide doses above 0.1 mg/day (Table 2). Dose response relationship was confirmed with $p < 0.0001$ for linear contrast. FPG levels also showed reductions with all liraglutide dose levels versus placebo ranging from 0.76 to 2.48 mmol/L, with $p < 0.0001$ for linear contrast. A reduction in FPG was already evident at the 2 week visit, which was the first timepoint following start of liraglutide administration.

Glucose levels following a standard breakfast after 14 weeks showed a significant dose response in glucose AUC_{0–}

Table 1 – Patient flow and baseline characteristics of treatment groups

Screened	372				
Screening failure					
Met ≥ 1 exclusion criterion	100				
Failed ≥ 1 inclusion criterion	39				
Other	15				
Randomized	Placebo 46	0.1 mg 45	0.3 mg 46	0.6 mg 45	0.9 mg 44
Withdrew					
Adverse event	1	0	0	0	1
Non compliance with protocol	0	1	1	0	0
Ineffective therapy	1	1	1	1	0
Other	6	0	1	0	1
Completed	38	43	43	44	42
Age (years)	57.5	56.5	56.8	60.0	55.5
Mean (S.D.)	(8.7)	(8.4)	(8.8)	(7.0)	(7.6)
Gender: male/female (n/n)	29/17	31/14	32/14	28/17	31/13
Body weight (kg), mean (S.D.)	62.78 (10.88)	64.82 (10.29)	62.42 (11.18)	61.97 (9.40)	62.36 (10.65)
BMI (kg/m^2), mean (S.D.)	23.77 (2.63)	24.26 (2.77)	23.93 (3.09)	23.74 (2.78)	23.59 (3.04)
Duration of diabetes (years), mean (S.D.)	7.48 (5.65)	7.15 (5.14)	6.78 (4.69)	8.87 (6.77)	7.62 (4.92)
Diabetic complications					
Retinopathy (n)	10	17	13	11	5
Nephropathy (n)	6	9	9	8	3
Neuropathy (n)	12	14	12	7	11
Other (n)	2	0	0	1	0
Treatment includes OAD (n)	22	21	22	19	20

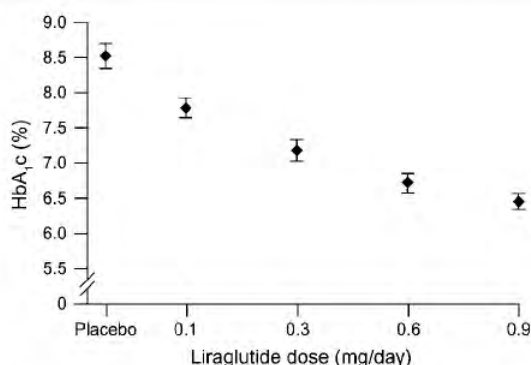


Fig. 1 – Dose-response for HbA_{1c} with increasing doses of liraglutide. Data are means ± S.E. for HbA_{1c} after 14 weeks.

3 h, with reductions versus placebo at all liraglutide dose levels and $p < 0.0001$ for linear contrast (Table 2). One hour PPG levels showed reductions with all liraglutide doses except for the lowest, while all liraglutide doses showed reductions in 2 and 3 h PPG versus placebo (Fig. 2).

Insulin levels during the 3 h following the standard breakfast were also increased by the three highest liraglutide dose levels (Table 2), also showing dose response ($p < 0.0001$

for linear contrast). This was accompanied by significant dose relationship in beta cell function (HOMA B), with increases versus placebo at 0.3, 0.6 and 0.9 mg/day liraglutide (also $p < 0.0001$ for linear contrast). Pro insulin:insulin ratio and pro insulin:C peptide ratios were decreased in all liraglutide dose groups ($p = 0.0008$ and $p < 0.0001$ for linear contrast, respectively). There was no evidence of change in insulin resistance (HOMA R).

No relevant changes in body weight occurred during the study, a reduction of 0.95 kg (from baseline 62 kg) occurring in the placebo group and changes in the liraglutide groups ranging from +0.13 kg to 0.48 kg versus baseline (Table 2).

No major hypoglycemic events were reported in any study group during the trial. Likewise, no episodes of minor hypoglycemia occurred (symptomatic events confirmed by plasma glucose < 3.1 mmol/L).

Plasma levels of liraglutide remained steady in all dose groups from 2 to 14 weeks; mean (S.D.) plasma concentrations at 14 weeks were 1.98 (0.93), 4.31 (1.68), 9.42 (4.13) and 10.08 (4.21) nmol/L in subjects receiving 0.1, 0.3, 0.6 and 0.9 mg/day liraglutide, respectively. No treatment related increase in liraglutide antibodies occurred during the study. An assay specific normal range was defined from a phase 2 study in Caucasians with type 2 diabetes [21]. In this trial of Japanese subjects, antibody levels were above the pre defined assay cut off level in 11/226 patients at baseline and in 13/207

Table 2 – Effect of liraglutide on measures of glycemia, beta-cell function and body weight

	Placebo	0.1 mg	0.3 mg	0.6 mg	0.9 mg	F test for linear contrast
HbA_{1c} (%), mean (S.D.)						
Baseline	8.43 (1.02)	8.50 (0.84)	8.24 (0.92)	8.21 (0.83)	8.12 (0.98)	
Week 14	8.52 (1.23)	7.78 (0.91)	7.17 (1.01)	6.71 (0.92)	6.45 (0.77)	
Liraglutide placebo, mean (95% CI)		0.79 (1.08, 0.50)	1.22 (1.50, 0.93)	1.64 (1.93, 1.35)	1.85 (2.14, 1.56)	$p < 0.0001$
Patients achieving HbA_{1c} levels at week 14, n (%)						
$< 5.8\%$	0 (0%)	0 (0%)	1 (2.2%)	6 (13.3%)	9 (20.5%)	
$\geq 5.8\%, < 6.5\%$	1 (2.2%)	3 (6.7%)	12 (26.1%)	18 (40.0%)	16 (36.4%)	
$\geq 6.5\%, < 7.0\%$	3 (6.5%)	7 (15.6%)	7 (15.2%)	4 (8.9%)	8 (18.2%)	
$\geq 7.0\%$	34 (73.9%)	33 (73.3%)	23 (50.0%)	15 (33.3%)	9 (20.5%)	Not applicable
7 point SMPG profile: AUC(7 point) (mmol/(L h)), mean (S.D.)						
Baseline	170.8 (32.0)	173.7 (32.0)	164.7 (32.2)	167.0 (35.1)	155.5 (27.7)	
Week 14	165.6 (35.1)	153.1 (30.3)	137.8 (29.0)	123.5 (23.6)	116.8 (27.4)	
Liraglutide placebo, mean (95% CI)		13.7 (25.3, 2.1)	25.0 (36.6, 13.3)	40.2 (51.9, 28.6)	41.9 (53.8, 29.9)	$p < 0.0001$
Fasting plasma glucose (mmol/L), mean (S.D.)						
Baseline	9.99 (1.71)	10.03 (1.73)	9.84 (1.73)	9.84 (1.23)	9.34 (1.36)	
Week 14	9.77 (2.47)	9.03 (1.76)	8.42 (1.96)	7.41 (1.23)	6.91 (1.22)	
Liraglutide placebo, mean (95% CI)		0.76 (1.40, 0.11)	1.26 (1.89, 0.61)	2.27 (2.92, 1.63)	2.48 (3.13, 1.82)	$p < 0.0001$
1 h postprandial plasma glucose (mmol/L), mean (S.D.)						
Baseline	16.91 (2.42)	16.57 (2.61)	16.08 (2.61)	16.47 (2.99)	15.61 (2.89)	
Week 14	16.03 (2.72)	15.00 (2.70)	13.78 (2.87)	12.99 (2.78)	11.39 (2.68)	
Liraglutide placebo, mean (95% CI)		0.83 (1.81, 0.15)	1.75 (2.73, 0.76)	2.78 (3.74, 1.81)	3.85 (4.84, 2.86)	Not tested
2 h postprandial plasma glucose (mmol/L), mean (S.D.)						
Baseline	15.97 (2.92)	16.05 (3.04)	14.77 (2.74)	16.01 (3.78)	14.42 (3.44)	
Week 14	14.95 (3.49)	13.57 (3.15)	11.48 (2.89)	10.74 (2.94)	8.89 (3.16)	

Table 2 (Continued)

	Placebo	0.1 mg	0.3 mg	0.6 mg	0.9 mg	F test for linear contrast
Liraglutide placebo, mean (95% CI)		1.43 (2.58, 0.29)	2.83 (3.98, 1.68)	4.22 (5.35, 3.09)	5.23 (6.39, 4.07)	Not tested
3 h postprandial plasma glucose mmol/L, mean (S.D.)						
Baseline	13.34 (2.91)	13.86 (3.09)	12.49 (2.96)	13.52 (3.48)	12.27 (2.92)	
Week 14	12.57 (3.10)	11.24 (2.68)	9.39 (2.86)	8.13 (2.28)	6.86 (1.88)	
Liraglutide placebo, mean (95% CI)		1.56 (2.53, 0.58)	2.79 (3.77, 1.82)	4.53 (5.49, 3.57)	5.23 (6.21, 4.26)	Not tested
AUC(0–3 h) plasma glucose (mmol/L h), mean (S.D.)						
Baseline	44.35 (6.88)	44.50 (7.19)	42.02 (6.72)	44.18 (8.54)	40.84 (7.85)	
Week 14	41.86 (8.19)	38.64 (7.40)	34.16 (7.12)	31.46 (6.39)	27.12 (6.41)	
Liraglutide placebo, mean (95% CI)		3.30 (5.88, 0.73)	6.42 (9.01, 3.84)	10.30 (12.85, 7.76)	12.80 (15.40, 10.20)	$p < 0.0001$
AUC (0–3 h) insulin (μ U/mL h), mean (S.D.)						
Baseline	58.84 (32.47)	54.12 (30.98)	71.69 (48.06)	60.53 (32.04)	63.83 (45.73)	
Week 14	59.38 (33.72)	64.23 (33.17)	95.29 (69.12)	102.56 (78.51)	88.97 (67.74)	
Liraglutide placebo, mean (95% CI)		10.69 (6.00, 27.39)	19.69 (3.01, 36.36)	41.34 (25.12, 57.55)	23.02 (6.52, 39.52)	$p < 0.0001$
Beta cell function (HOMA β) (μ U/mL)/(mg/dL), mean (S.D.)						
Baseline	21.45 (14.75)	19.36 (13.34)	23.97 (18.51)	22.06 (13.69)	22.99 (18.62)	
Week 14	22.34 (21.77)	27.56 (19.39)	36.82 (28.16)	44.06 (30.27)	44.04 (32.44)	
Liraglutide placebo, mean (95% CI)		7.79 (0.11, 15.70)	11.40 (3.58, 19.21)	20.99 (13.17, 28.80)	19.82 (11.96, 27.67)	$p < 0.0001$
Insulin resistance (HOMA R), mean (S.D.)						
Baseline	2.78 (1.90)	2.68 (1.69)	3.02 (2.00)	2.93 (1.63)	2.58 (1.86)	
Week 14	2.35 (1.33)	2.82 (1.98)	3.34 (3.12)	2.61 (1.81)	2.05 (1.47)	
Liraglutide placebo, mean (95% CI)		0.54 (0.15, 1.23)	0.83 (0.15, 1.51)	0.14 (0.54, 0.82)	0.17 (0.85, 0.52)	$p = 0.3521$
Pro insulin:insulin ratio (pmol/L)/(μ U/mL), mean (S.D.)						
Baseline	1.56 (1.32)	1.52 (1.17)	1.44 (1.03)	1.50 (1.27)	1.51 (1.01)	
Week 14	1.58 (1.25)	1.04 (0.66)	1.04 (0.77)	0.86 (0.65)	1.00 (0.94)	
Liraglutide placebo, mean (95% CI)		0.53 (0.87, 0.20)	0.50 (0.83, 0.17)	0.69 (1.02, 0.36)	0.56 (0.89, 0.23)	$p = 0.0008$
Pro insulin:C peptide ratio (pmol/L)/(ng/mL), mean (S.D.)						
Baseline	4.28 (2.90)	3.98 (2.45)	4.05 (2.28)	4.16 (3.56)	3.60 (1.97)	
Week 14	3.87 (2.32)	3.22 (2.35)	2.94 (2.08)	2.41 (1.47)	2.28 (1.53)	
Liraglutide placebo, mean (95% CI)		0.54 (1.25, 0.18)	0.84 (1.55, 0.13)	1.40 (2.11, 0.69)	1.32 (2.04, 0.61)	$p < 0.0001$
Body weight (kg), mean (S.D.)						
Baseline	62.00 (10.97)	64.26 (10.46)	61.54 (10.98)	61.52 (9.46)	61.48 (10.55)	
Week 14	61.05 (10.89)	64.21 (10.67)	61.67 (11.39)	61.42 (9.68)	61.00 (11.07)	
Liraglutide placebo, mean (95% CI)		0.87 (0.19, 1.55)	1.08 (0.41, 1.75)	0.84 (0.16, 1.51)	0.46 (0.22, 1.14)	$p = 0.2481$

Values for baseline and week 14 are mean (S.D.). Liraglutide placebo differences (at week 14) were calculated using an ANOVA model with dose group and pre treatment as fixed effects and baseline value as covariate. SMPG, self measured plasma glucose.

patients at week 15 (post treatment). No subject's antibody levels at week 15 exceeded the maximum level recorded at baseline.

A total of 154 patients (68%) experienced adverse events during the study, most commonly infections and gastro intestinal disorders. Distribution of adverse events was similar across treatment groups for infection/infestation disorders; incidences of gastrointestinal disorders were placebo, 24%; liraglutide 0.1 mg/day, 18%; 0.3 mg/day, 15%; 0.6 mg/day, 31%; 0.9 mg/day, 30%. Two patients, one receiving placebo, and one receiving 0.9 mg/day liraglutide, withdrew due to adverse

events (abdominal discomfort and viral gastroenteritis; upper abdominal pain, respectively).

Seven patients entering the study experienced serious adverse events; in five cases these events occurred before receiving any study medication. The two remaining events concerned a subject with suspected papillary thyroid carcinoma (in the 0.6 mg/day liraglutide group) and a subject who suffered an alcohol related fall (in the 0.9 mg/day liraglutide group). Neither event was considered by investigators to be related to study treatment and both patients completed the study.

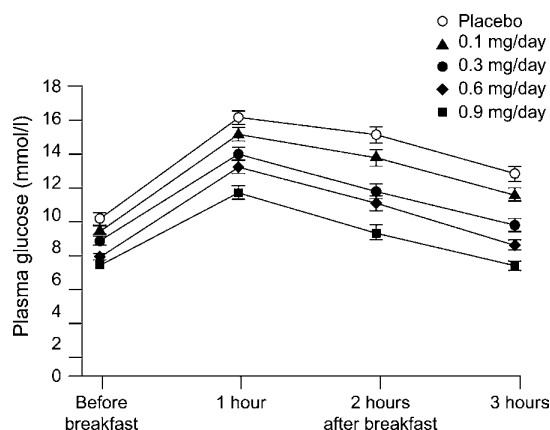


Fig. 2 – Postprandial plasma glucose profiles following a standard breakfast after 14 weeks' treatment with liraglutide. Data are means $\pm$ S.E.

4. Discussion

In this study, we investigated efficacy and safety from a dose response perspective with four doses of liraglutide and placebo in Japanese patients with type 2 diabetes. We demonstrated significantly dose dependent improvements in key parameters of glycemia: HbA_{1c} , FPG, PPG, seven point self monitored plasma glucose and beta cell function following 14 weeks' treatment with liraglutide. Treatment was weight neutral, no major or minor hypoglycemic episodes occurred, and there was no treatment related development of liraglutide antibodies during the trial.

The magnitude of HbA_{1c} reduction with liraglutide in this study is comparable to those reported in non Japanese subjects by Vilsbøll and colleagues, where reductions of up to 1.74% points were achieved from similar baseline HbA_{1c} levels of 8.1–8.5% [14]. Madsbad and colleagues reported a 0.74% point reduction in HbA_{1c} with liraglutide, 0.75 mg/day, from a somewhat better controlled baseline of 7.4% [13].

A clear dose response relationship for HbA_{1c} reduction was shown in this study. All doses of liraglutide tested showed a degree of efficacy, with a plateau of dose response at 0.9 mg/day. A dose of 0.9 mg/day appears to be highly effective and, of the doses tested, offers the optimal efficacy/tolerability balance in Japanese patients with type 2 diabetes. Indeed, the reductions in HbA_{1c} in this study allowed a large majority of patients receiving the higher doses of liraglutide to achieve satisfactory glycaemic control: in the 0.9 mg/day group 75% of patients achieved $HbA_{1c} < 7.0\%$ and more than 50% achieved $HbA_{1c} < 6.5\%$ ('good' or 'excellent' categories in current Japan Diabetes Society guidance) without safety concerns or limited tolerability [22]. As in previous studies with liraglutide in non Japanese subjects [7,12,13,21], the risk of hypoglycemia is low with this agent, with no confirmed minor or major hypoglycemic episodes reported in this study. This combination of efficacy and hypoglycemic tolerability is highly encouraging.

Previous longer term studies with liraglutide, largely in Caucasians, have reported significant weight reduction [7,12,14]. In the present study, body weight remained stable.

This is likely to reflect the very different initial characteristics typical for Japanese patients: initial BMI values in the studies by Feinglos et al. and Nauck et al. were 34.5 kg/m² and 31.3 kg/m², respectively, compared with 23.9 kg/m² in our Japanese cohort [7,12].

Japanese and Caucasian patients also differ, typically, in the nature of their type 2 diabetes. Japanese subjects have greatly impaired first phase insulin secretion from an early stage in type 2 diabetes, which accelerates the onset of postprandial hyperglycemia, whereas in some other groups type 2 diabetes is a disease of profound insulin resistance [23–26]. The improvements in overall metabolic control as well as in PPG levels with liraglutide in Japanese individuals are therefore welcome and consistent with previous data with liraglutide in non Japanese subjects [15]. Taken together, these data show that liraglutide is highly effective in populations where either increased insulin resistance or impaired insulin secretion is the main contributor to metabolic derangement. The 31% reduction in postprandial glucose AUC seen in this study with 0.9 mg/day liraglutide compares favorably with the 23% reduction reported in Caucasian subjects by Juhl et al. [15]. Evidence from this study of improvements in beta cell function was also encouraging. Pro insulin:insulin ratio, a postulated indicator of insulin secretory dysfunction [27,28] was reduced by all doses of liraglutide versus placebo, as seen in previous studies with liraglutide [13]. Beta cell function (HOMA B) was improved by liraglutide, as seen by Madsbad et al. [13]; the lack of improvement in HOMA R is likely to reflect the lack of effect on body weight and the low initial levels of insulin resistance in these Japanese subjects.

Liraglutide was well tolerated in this study, with adverse event profiles comparable to placebo and few withdrawals from treatment. No safety concerns were raised.

In conclusion, we have shown that liraglutide, at doses of up to 0.9 mg/day, is effective in improving glycaemic control and well tolerated in Japanese patients with type 2 diabetes, with encouraging indications of beneficial effects on beta cell function. An agent that allows three quarters of a population of subjects with type 2 diabetes to achieve good glycaemic control, with a low risk of hypoglycemia and no weight gain, is well tolerated and requires only a single daily administration will be welcome in clinical practice.

Conflict of interest statement

We have a competing interest to declare. Professor Seino and Professor Kaku and currently on an advisory board for Novo Nordisk Pharma Ltd., Tokyo, Japan. Mads Rasmussen is employed by, and holds shares in, Novo Nordisk A/S, Copenhagen, Denmark.

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Appendix A. Investigators

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