

## Liraglutide for the treatment of diabetes mellitus in Japan

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### Practice Points

- A once-daily 0.9 mg dose of liraglutide administered to Japanese subjects with Type 2 diabetes mellitus provides a significant glycated reduction hemoglobin of 1.5% or more from the baseline with few hypoglycemic episodes.
- Stepwise dose titration by 0.3-mg increments at intervals of 1 week significantly reduces the frequency of gastrointestinal symptoms.
- When liraglutide is used in combination with sulfonylurea, dose reduction of sulfonylurea should be considered to avoid a risk of hypoglycemia.
- A once-daily 0.9-mg dose of liraglutide is not always sufficient to suppress bodyweight gain.
- The use of liraglutide in insulin-dependent patients should be strictly avoided.
- The safety of liraglutide is not established in pregnant patients or in pediatric patients.

**SUMMARY** Impaired  $\beta$ -cell function in Type 2 diabetes mellitus (T2DM) is generally progressive. The commonly used sulfonylureas (SU) lose efficacy over time and are associated with impaired  $\beta$ -cell function, and undesirable events such as weight gain and hypoglycemia. Thus, there is a strong need to develop antidiabetic agents that control glycemia without weight gain and hypoglycemia, and preserve  $\beta$ -cell function. Glucagon-like-peptide-1 (GLP-1) is known to improve glycemic control by enhancement of glucose-stimulated insulin secretion, preserving  $\beta$ -cell function, and minimizing hypoglycemia and weight gain. Liraglutide, a human GLP-1 analog, has recently been approved for use in Japanese patients with T2DM. To assess liraglutide in management of Japanese patients with T2DM, the results of clinical studies in Japan is summarized and also compared with the data from Europe and the USA. Clinical studies have shown liraglutide to be effective in achieving and maintaining glycemic control, while restoring insulin secretion in Japanese patients. In the Japanese Phase III studies, liraglutide demonstrated significant reductions in glycated hemoglobin ( $HbA_{1c}$ ) levels and body weight in patients with T2DM. When liraglutide was given as monotherapy  $HbA_{1c}$  was reduced from baseline by 1.74% with liraglutide versus 1.18% with glibenclamide, at 24 weeks. When combined with a sulfonylurea, the mean change in  $HbA_{1c}$  from baseline to

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week 24 was -1.56% with liraglutide 0.9 mg/day versus -0.40% with placebo. It is noteworthy that Japanese patients with T2DM had similar or better improvements in blood glucose levels when administered a dose half that used in the USA and Europe. The dose titration (initiated with a dose of 0.3 mg once daily and increased by 0.3-mg increments at intervals of at least 1 week) significantly reduced the frequency of gastrointestinal symptoms and is not effective for glycemic control. When liraglutide is added to a SU, the SU dose reduction is recommended and the daily dose of liraglutide increased cautiously to avoid hypoglycemic episodes. On the other hand, acute hyperglycemia and diabetic ketoacidosis has been reported in patients who switched from insulin to liraglutide in Japan. The use of liraglutide in insulin-dependent patients should be strictly avoided. The GLP-1 receptor agonist liraglutide has excellent efficacy and tolerability in Japanese patients with T2DM, with superior effects than those observed in Western patients. It is strongly expected that liraglutide will play a major role in the treatment of diabetes mellitus in Japan.

The global incidence of Type 2 diabetes mellitus (T2DM) is increasing due to rising rates of obesity and resulting insulin resistance. In 2005 an estimated 220 million people worldwide had diabetes, of which approximately 90% had T2DM [101]. The number of deaths from diabetes was approximately 1.1 million in 2005 and is expected to double by 2030 [101]. While the greatest increases in incidence and mortality are occurring in Western populations, Asian countries are experiencing rapidly rising rates of T2DM due to adoption of Western lifestyles. A 2007 survey conducted by the Japanese Ministry of Health, Labour and Welfare reported that approximately 8.9 million Japanese people had diabetes, an increase from the 6.9 million reported in 1997 [102]. In 2007, 13,971 Japanese patients died from diabetes, a mortality rate of 11.1 per 100,000 [102].

Lifestyle changes are responsible for the dramatic increase in incidence of T2DM in Japan. As a result of their historically vegetarian diet and from their pancreatic  $\beta$ -cell vulnerability, Asians' normal insulin secretion is approximately half that of Caucasians [1,2]. The pathophysiology of T2DM in Asians, including Japanese people, is also different compared with Caucasians. While T2DM in Caucasians is significantly associated with insulin resistance, insulin sensitivity is relatively maintained in Japanese patients with T2DM [1,2]. Thus, it is thought that failure of insulin secretion has been primarily responsible for the onset of T2DM in Japanese people. However, the incidence and pathophysiology of T2DM in the Japanese are changing due to changes in diet and exercise habits in recent decades. 'Westernization' of the Japanese diet has increased consumption of animal products and extensive use of automobiles has led

to decreased physical exercise. Accumulation of visceral fat increases insulin resistance. Because Japanese people have low insulin secretion, even a small weight increase may trigger development of T2DM.

Impaired insulin secretion associated with loss of functional  $\beta$ -cell mass is generally progressive [3,4] and its progression involves glucose toxicity and lipotoxicity. Studies involving Japanese patients have also reported that pancreatic  $\beta$  cell mass is reduced by 30% in diabetic patients versus nondiabetic subjects [5].

Minimizing the risks of weight gain and hypoglycemia and maintaining pancreatic  $\beta$ -cell function are certainly key goals in treating all T2DM patients, however, maintaining pancreatic  $\beta$ -cell function and insulin secretion is particularly important in Japanese T2DM patients. Sulfonylurea (SU) drugs have been the most commonly used oral antidiabetic agents (OADs) in Japan, but their efficacy in glycemic control generally decreases over time [6,7]. Additionally, SUs are associated with greater impairment of  $\beta$ -cell function, weight gain and hypoglycemia, compared with metformin and glitazones [6,7]. The possibility of adverse effects on cardiac function has also been pointed out [8].

New therapies targeting the incretin system have the potential to improve glycemic control, preserve  $\beta$ -cell function, and minimize hypoglycemia and weight gain [9]. Incretins are gastrointestinal hormones that stimulate insulin secretion. They are secreted from the small intestine when food is ingested. Currently, glucagon-like-peptide-1 (GLP-1) and gastric inhibitory polypeptide are known as incretins. GLP-1 stimulates insulin secretion and inhibits glucagon secretion, thereby improving blood glucose levels. At the same time, GLP-1

suppresses appetite and slows gastric emptying, therefore contributing to weight reduction to some degree [10]. In T2DM, insulin response of  $\beta$  cells to GLP-1 is impaired [10,11]. GLP-1 receptor agonists, including liraglutide (Victoza®, Novo Nordisk) have shown promise in achieving these treatment goals [8,12–15]. Administration of a GLP-1 receptor agonist that greatly exceeds blood levels of intrinsic GLP-1 overcomes this impairment, restoring insulin secretion and improving glycemic control [9,16,17]. Liraglutide has recently been approved for treatment of T2DM in Japan following completion of Phase III trials demonstrating its efficacy and safety in this population [13,14].

Insulin secretion deficiency, rather than insulin resistance, is considered the dominant mechanism in the pathology of T2DM in the Japanese. GLP-1 receptor agonists may be suitable therapy for Japanese patients with T2DM characterized by insulin secretion deficiency. To assess the clinical usefulness of liraglutide in Japanese patients with T2DM, this report summarizes the results of clinical studies conducted in Japan, and briefly compares the differences with data from Europe and the USA.

### Indications & usage

In Japan, liraglutide is indicated for the treatment of patients with T2DM in whom sufficient glycemic control has not been achieved with diet and exercise alone, or with SU therapy in combination with diet and exercise [13,14]. Liraglutide may be used as a monotherapy or in combination with a SU.

### Dosage & administration

Usually, in adults, 0.9 mg of liraglutide is subcutaneously administered once daily in the morning or evening. Liraglutide should be initiated with a dose of 0.3 mg once daily and increased by 0.3-mg increments at intervals of at least 1 week. Titrating gradually from a low dose is intended to reduce the frequency of gastrointestinal symptoms and is not effective for glycemic control. The dose should be adjusted according to the patient's gastrointestinal symptoms, up to a maximum dose of 0.9 mg. In patients experiencing adverse effects at the usual dose of 0.9 mg, the dose should be reduced to 0.6 mg. If symptoms persist at this dose, the drug should be stopped. A dose of 0.9 mg liraglutide can be reintroduced if symptoms resolve within 1–2 days.

### Clinical pharmacology

#### ■ Mechanism of action

Liraglutide is a human GLP-1 receptor agonist with 97% amino acid sequence homology to endogenous human GLP-1 (7–37), with an arginine substituted for lysine at position 34 (Figure 1). Liraglutide activates the GLP-1 receptor in pancreatic  $\beta$  cells. Through this action, liraglutide, as well as native human GLP-1, increases cyclic AMP, which stimulates insulin secretion in a glucose-dependent manner. As blood glucose concentrations decrease in response to the insulin, insulin secretion decreases. Liraglutide also decreases glucagon secretion from pancreatic  $\alpha$  cells when blood glucose concentrations are high. The blood glucose lowering is accompanied by a delay in gastric emptying [9,15].

Endogenous GLP-1 has a half-life of only 1.5–2 min owing to degradation by the endogenous enzymes dipeptidyl peptidase IV (DPP-4) and neutral endopeptidases [10]. By contrast, liraglutide is stable against degradation by DPP-4 and neutral endopeptidases and has a plasma half-life of 13 h after subcutaneous administration [18].

#### ■ Pharmacodynamics

Following once-daily administration, liraglutide lowers fasting, premeal and postprandial glucose concentrations throughout the day. Plasma blood glucose was measured in 15 Japanese subjects with T2DM after subcutaneous administration of multiple doses of placebo or 5 or 10  $\mu$ g/kg (corresponding to 0.3 and 0.6 mg for a 60 kg person, respectively) of liraglutide with stepwise weekly dose increases once daily for 14 days. Compared to the placebo group, the plasma

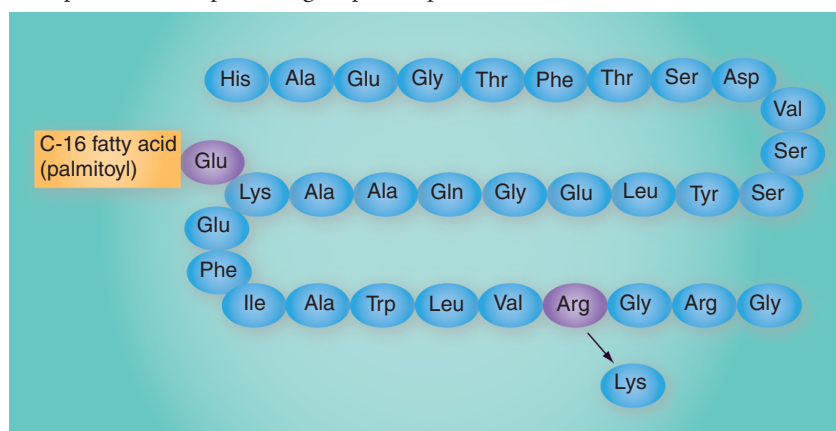


Figure 1. Liraglutide.

blood glucose (area under the curve [AUC]<sub>glucose, 0–24h</sub>/24) in patients receiving liraglutide was 20% lower in the 5- $\mu\text{g/kg}$  group and 31% lower in the 10- $\mu\text{g/kg}$  group. The plasma insulin (AUC<sub>insulin, 0–24h</sub>/24) was 23% higher in the 5- $\mu\text{g/kg}$  group and 99% higher in the 10- $\mu\text{g/kg}$  group, compared with the placebo group [19].

### ■ Pharmacokinetics

#### Healthy volunteers

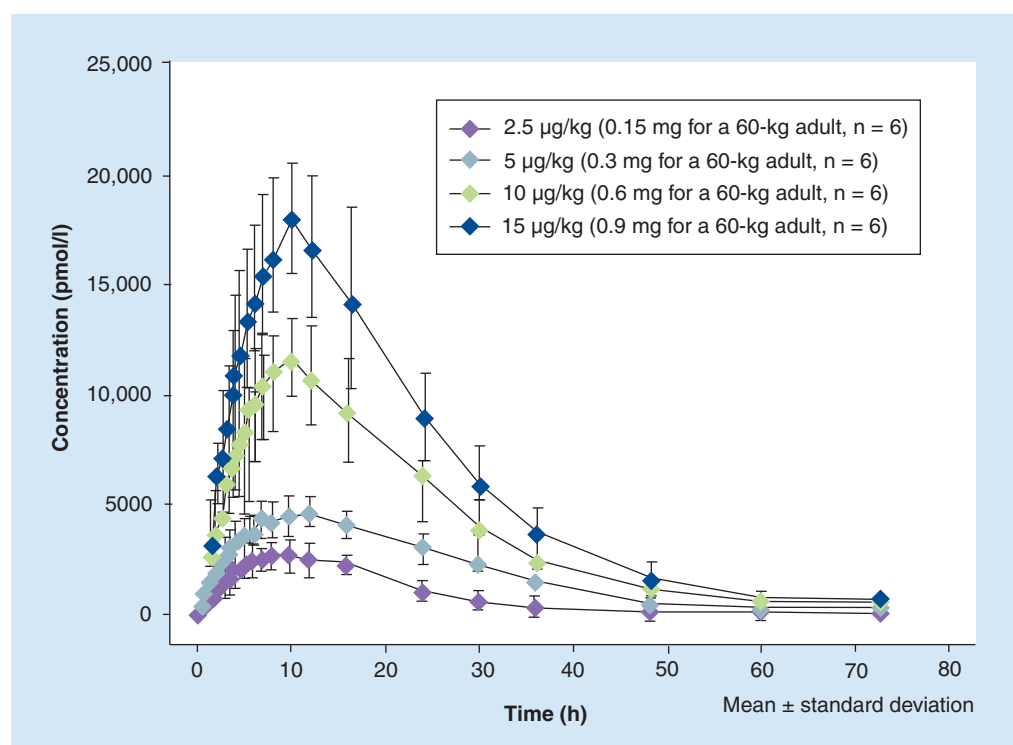
Healthy adult male Japanese volunteers were administered a single dose of liraglutide ( $n = 24$ ) at 2.5, 5.0, 10 or 15  $\mu\text{g/kg}$  (corresponding to 0.15, 0.3, 0.6 and 0.9 mg for a 60 kg person, respectively) or placebo ( $n = 8$ ) by subcutaneous injection. Liraglutide was absorbed slowly, reaching maximum concentration ( $C_{\text{max}}$ ) at a median 7.5–11 h after administration, followed by monophasic elimination (Figure 2). The elimination half-life was a mean 10–11 h. The AUC and  $C_{\text{max}}$  increased proportionately to the liraglutide dose [19].

Healthy male Japanese volunteers were administered liraglutide ( $n = 18$ ) at 5, 10 or 15  $\mu\text{g/kg}$  (corresponding to 0.3, 0.6 and 0.9 mg

for a 60 kg person, respectively) or placebo ( $n = 6$ ) as repeated subcutaneous injections once daily for 21 days, with a weekly dose increase of 5  $\mu\text{g/kg}$ . The time to maximal concentration ( $t_{\text{max}}$ ) was a median 8–9 h and half-life ( $t_{1/2}$ ) was 13.4–14 h, with monophasic elimination. The AUC and  $C_{\text{max}}$  of liraglutide increased proportionately to the liraglutide dose. From the trough concentration, it was observed that steady state plasma concentration was reached relatively rapidly [19].

#### Subjects with T2DM

Japanese patients with T2DM were administered repeated doses of liraglutide ( $n = 12$ ) at 5 or 10  $\mu\text{g/kg}$  (corresponding to 0.3 and 0.6 mg for a 60 kg person, respectively) or placebo ( $n = 4$ ) once daily for 14 days with a weekly dose increase of 5  $\mu\text{g/kg}$ .  $t_{\text{max}}$  was a median 9–12 h and  $t_{1/2}$  was 14–15 h, with monophasic elimination. The AUC and  $C_{\text{max}}$  after the last administration in the 10- $\mu\text{g/kg}$  group were about twice that in the 5- $\mu\text{g/kg}$  group. Other parameters were almost constant, regardless of the dose [19].



**Figure 2.** Change in blood concentrations and pharmacokinetic parameters after a single liraglutide dose in Japanese healthy adults.

Data taken from [19].

**Table 1. Liraglutide pharmacokinetic parameters in subjects with hepatic impairment.**

Hepatic impairment severity	AUC <sub>0-inf</sub> ratio (90% CI)	C <sub>max</sub> ratio (90% CI)	t <sub>1/2</sub> (h) ratio (90% CI)
Mild/normal	0.77 (0.53, 1.11)	0.89 (0.65, 1.21)	0.95 (0.83, 1.10)
Moderate/normal	0.87 (0.60, 1.25)	0.80 (0.59, 1.09)	1.01 (0.88, 1.17)
Severe/normal	0.56 (0.39, 0.81)	0.71 (0.52, 0.97)	0.85 (0.73, 0.98)

Subjects with normal hepatic function or subjects with mild, moderate and severe hepatic impairment (n = 6 for each group) received a 0.75-mg single dose of liraglutide. Severity of hepatic impairment was classified by Child–Pugh scores: mild, grade A (5–6 points); moderate, grade B (7–9 points); severe, grade C (10–15 points). The statistical analysis was adjusted for effects of age, gender and weight.  
AUC<sub>0-inf</sub>: Area under the curve; C<sub>max</sub>: Maximum concentration; t<sub>1/2</sub>: Half-life.  
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### Elderly subjects

The pharmacokinetics of liraglutide after a single 1-mg dose were compared between healthy elderly (65–83 years; n = 16) and young (21–45 years; n = 16) subjects. For elderly versus young subjects, the estimated AUC<sub>0-t</sub> ratio was 0.94 (90% confidence interval [CI]: 0.84–1.06) and the estimated C<sub>max</sub> ratio was 0.94 (90% CI: 0.84–1.05). No significant difference was observed between young and elderly subjects [20].

### Subjects with hepatic impairment

The pharmacokinetics of liraglutide after a single dose were compared among six healthy subjects and 18 subjects with mild, moderate or severe hepatic impairment, according to the Child–Pugh classification [21]. The subjects received a single dose of 0.75 mg liraglutide administered subcutaneously. The primary end point was AUC<sub>0-inf</sub>. The mean AUC<sub>0-inf</sub> was lowest in patients with severe hepatic impairment and highest in healthy subjects (0.56, 90% CI: 0.39–0.81). The AUC<sub>0-inf</sub>, C<sub>max</sub> and t<sub>1/2</sub> ratios for hepatic impaired/nonimpaired subjects are shown in Table 1. Liraglutide was well tolerated in all groups, with no adverse events, hypoglycemic episodes, or clinically significant changes in laboratory parameters. The results demonstrate that exposure to liraglutide decreases with increasing hepatic impairment. However, the relationship between dose increase and adverse events has not been

clarified. Therefore, T2DM patients with hepatic impairment should be treated with the standard dose of liraglutide.

### Subjects with renal impairment

The pharmacokinetics of liraglutide after one 0.75 mg subcutaneous dose were compared in 30 subjects, six of whom had normal renal function and 24 of whom had mild (n = 6), moderate (n = 7) or severe (n = 5) renal impairment or end-stage renal disease (ESRD) (n = 6) [22]. The ESRD group included patients on continuous ambulatory peritoneal dialysis but patients on hemodialysis or with renal transplant were excluded. The primary end point was AUC<sub>0-inf</sub>. Comparisons between patients with renal impairment and normal renal function did not demonstrate equivalence according to the pre-defined criteria for 90% CI. There were no consistent trends in liraglutide AUC<sub>0-inf</sub> and C<sub>max</sub> with decreasing renal function. Table 2 shows the AUC<sub>0-inf</sub>, C<sub>max</sub> and t<sub>1/2</sub> ratios for subjects with mild to severe renal impairment and ESRD or subjects without renal impairment. Thus, we can expect that T2DM patients with renal impairment, including ESRD, will be able to use standard treatment regimens for liraglutide without dose adjustments.

### Clinical evidence

Liraglutide was shown to be safe and effective for the treatment of T2DM in Phase III trials conducted in Western countries [15]. In Japan,

**Table 2. Liraglutide pharmacokinetic parameters in subjects with renal impairment.**

Renal impairment severity	AUC <sub>0-inf</sub> ratio (90% CI)	C <sub>max</sub> ratio (90% CI)	t <sub>1/2</sub> (h) ratio (90% CI)
Mild/normal	0.67 (0.54, 0.85)	0.75 (0.57, 0.98)	0.79 (0.68, 0.91)
Moderate/normal	0.86 (0.70, 1.07)	0.96 (0.74, 1.23)	0.79 (0.69, 0.91)
Severe/normal	0.73 (0.57, 0.94)	0.77 (0.57, 1.03)	0.79 (0.68, 0.93)
ESRD/normal	0.74 (0.56, 0.97)	0.92 (0.67, 1.27)	0.71 (0.60, 0.84)

Subjects with normal renal function (n = 6) or subjects with mild (n = 6), moderate (n = 7), severe (n = 5) or ESRD (n = 6) received a 0.75-mg single dose of liraglutide. Renal impairment was classified by: mild, creatinine clearance rate (CCR) 50–80 ml/min; moderate, CCR 30–50 ml/min; severe, CCR less than 30 ml/min; ESRD, required hemodialysis. The statistical analysis was adjusted for effects of age and weight.  
AUC<sub>0-inf</sub>: Area under the curve; C<sub>max</sub>: Maximum concentration; ESRD: End-stage renal disease; t<sub>1/2</sub>: Half-life.  
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one dose–response study [12] and two long-term clinical trials have demonstrated the safety and effectiveness of liraglutide in Japanese patients with T2DM. One of the long-term clinical trials evaluated monotherapy with liraglutide versus glibenclamide [13]. The second investigated liraglutide as add-on therapy to a SU [14]. The HbA<sub>1c</sub> values used in the trials were based on the Japanese Diabetes Society standard [23].

### ■ Clinical trials

#### Dose–response study

A dose–response study in Japanese patients with T2DM was conducted to assess the efficacy, safety, and optimal dose of liraglutide during sustained treatment. Following an 8-week run-in period and discontinuation of any OADs, 226 patients were randomized to liraglutide 0.1 mg/day (n = 45), 0.3 mg/day (n = 46), 0.6 mg/day (n = 45), 0.9 mg/day (n = 44), or placebo (n = 46). Liraglutide doses in the 0.6- and 0.9-mg/day groups were increased from a starting dose of 0.3–0.6 mg/day after 1 week and by a further 0.3 mg/day in the 0.9-mg/day group after 2 weeks. The primary efficacy end point was HbA<sub>1c</sub> after 14 weeks of treatment.

The results showed that a liraglutide dose of 0.9 mg/day improved HbA<sub>1c</sub> to <7.0% in 75% and <6.5% in 57% of patients, with no major or minor hypoglycemic events [12]. Because patients achieved sufficient improvement with this dose, liraglutide 0.9 mg/day was determined to be the standard dose in Japan.

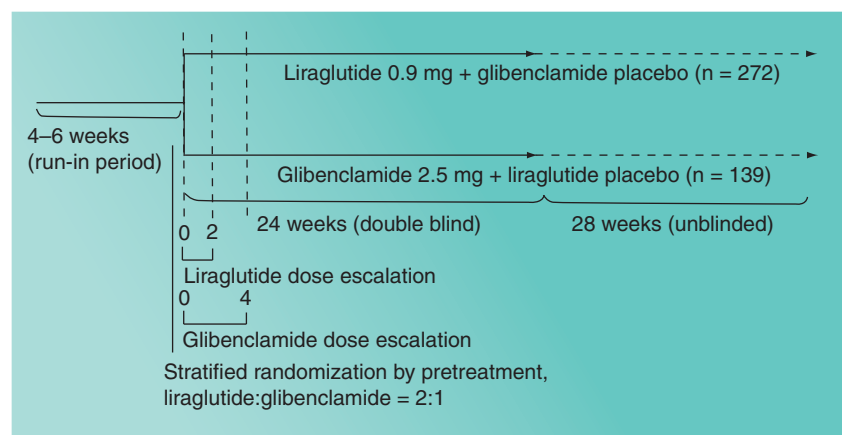
#### Liraglutide monotherapy

The aim of this randomized, Phase III trial was to compare the safety and efficacy of liraglutide versus glibenclamide monotherapy in Japanese patients with T2DM that was not adequately controlled with diet therapy or OAD monotherapy [13]. Following a 4–6 week wash-out period, 411 patients were stratified by pretreatment and randomized 2:1 to receive either once daily liraglutide 0.9 mg (n = 268) or glibenclamide 2.5 mg administered once or twice daily (n = 132) (Figures 3 & 4). Liraglutide was initiated at 0.3 mg/day and escalated during a 2-week period to 0.9 mg/day by weekly increments of 0.3 mg. Glibenclamide was started at 1.25 mg/day and increased after 4 weeks to 2.5 mg/day.

The primary efficacy end point was HbA<sub>1c</sub> at 24 weeks. Secondary end points included fasting plasma glucose (FPG), seven-point self-measured plasma glucose profiles, postprandial plasma glucose, body weight, lipid profile, and biomarkers for cardiovascular effects. Safety end points included the incidence of adverse events (AEs), vital signs, clinical laboratory assessments, and self-reported incidence of hypoglycemic episodes.

The efficacy results are summarized in Table 3. At 24 weeks, the mean HbA<sub>1c</sub> was 6.99% in the liraglutide group versus 7.50% in the glibenclamide group, demonstrating the superiority of liraglutide, with a difference between treatments of 0.50% (95% CI: -0.70 to -0.30; p < 0.0001). The change in HbA<sub>1c</sub> from baseline was -1.74% (SD ± 1.06) in the liraglutide group and -1.18% (SD ± 1.03) in the glibenclamide group (Figure 5). Bodyweight also was improved from baseline with liraglutide (-1.0 kg) versus glibenclamide (+0.91 kg; p < 0.0001). There was significant improvement in the liraglutide group versus the glibenclamide group in FPG (p < 0.0001), postprandial plasma glucose (p < 0.0001), Brain natriuretic peptide (p < 0.0001), and high sensitivity C-reactive protein (p = 0.0476). The estimated mean of free fatty acids in the liraglutide group (0.59 mEq/l [standard error ± 0.015]) was significantly lower than in the glibenclamide group (0.64 mEq/l [standard error ± 0.020]; p = 0.0252), but there was no significant difference in other lipid parameters.

Treatment emergent adverse events were reported in 73.1% of the liraglutide group and 74.2% of the glibenclamide group. The most common AEs in both treatment groups



**Figure 3. Liraglutide monotherapy trial design (Phase III trial conducted in Japan).**

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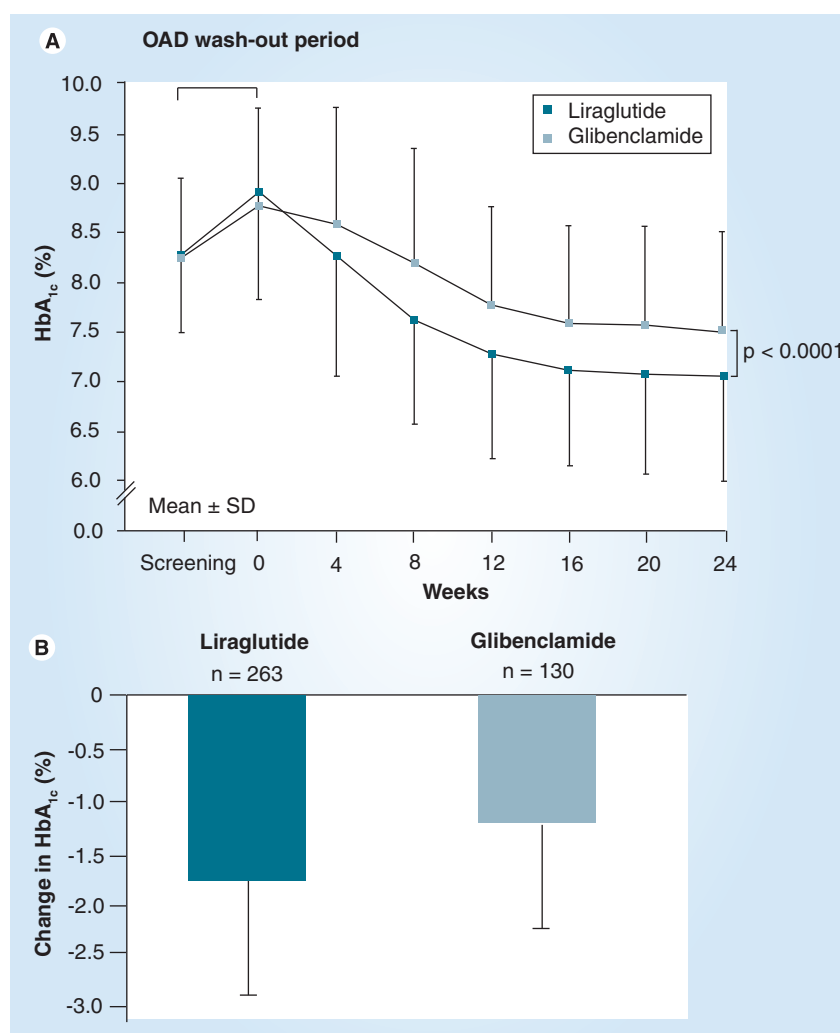
were nasopharyngitis, diarrhea, constipation and upper respiratory tract infection. Gastrointestinal AEs were more frequent with liraglutide than glibenclamide, including diarrhea (6.3 vs 3.8%), constipation (5.6 vs 3.8%), and nausea (4.5 vs 1.5%). Serious AEs were reported in 4.9% of liraglutide patients and 6.1% of glibenclamide patients. No major hypoglycemic episodes were reported in either group. Minor hypoglycemic episodes occurred less frequently with liraglutide than glibenclamide ( $p < 0.0001$ ) (Figure 5).

#### Liraglutide with SU

The objective of this Phase III trial was to evaluate the efficacy and safety of two doses of liraglutide compared with placebo, as add-on therapy to a SU [14]. A total of 264 Japanese patients with T2DM currently receiving SU therapy for at least 8 weeks were included in the study. After a 4-week run-in period, the patients were stratified according to pretrial SU therapy and randomized to liraglutide 0.6 or 0.9 mg/day or to placebo, in addition to the SU drug. Liraglutide was initiated at 0.3 mg/day and escalated during a 2-week period to 0.6 mg/day or to 0.9 mg/day by weekly increments of 0.3 mg (Figure 6).

The primary efficacy end point was  $HbA_{1c}$  at 24 weeks. Secondary end points included seven-point self-measured plasma glucose profiles, body weight, FPG, mean postprandial plasma glucose, lipid profile, and biomarkers for cardiovascular effects. Safety end points included incidence of hypoglycemic episodes and adverse events, vital signs, and laboratory assessments. The efficacy results are summarized in Table 4. Treatment with liraglutide 0.6 and 0.9 mg/day significantly reduced and sustained  $HbA_{1c}$  levels compared with placebo ( $p < 0.0001$ ) (Figure 7). Other parameters also were significantly improved with liraglutide versus placebo, including mean seven-point self-measured plasma glucose, FPG, brain natriuretic peptide and high sensitivity C-reactive protein (liraglutide 0.6 mg/day). No significant difference was observed between treatment groups in any of the lipid parameters.

Treatment emergent adverse events were reported in 76.1% of the liraglutide 0.6 mg/day group, 78.4% of the 0.9 mg/day group, and 75% of the placebo group. The most common AEs were nasopharyngitis, diarrhea and constipation. No major hypoglycemic episodes were



**Figure 4.**  $HbA_{1c}$  levels in the liraglutide monotherapy trial.  $HbA_{1c}$  over time (A) and mean change from baseline (B) in all subjects in the liraglutide monotherapy trial.  $HbA_{1c}$ : Glycated hemoglobin; OAD: Oral antidiabetic agent. Reproduced with permission from [13].

reported. The rate of minor hypoglycemic events was higher in both liraglutide groups than in the placebo group.

#### Adverse reactions

Gastrointestinal disturbances are often observed in patients treated with GLP-1 receptor agonists such as liraglutide. Native GLP-1 is known to inhibit the peristaltic motion of the gastrointestinal tract and to slow gastric emptying. Administering an exogenous GLP-1 receptor agonist at a high concentration leads to increased incidence of these effects, including nausea, constipation and diarrhea. In clinical studies conducted in Japan, these adverse gastrointestinal reactions were also reported; however,

Table 3. Metabolic parameters and cardiovascular biomarkers at 24 weeks in liraglutide monotherapy trial.						
End point	Mean at baseline (all subjects)	Treatment group	n	Week 24 (LOCF) LS mean (SE)	Treatment difference liraglutide –glibenclamide, mean (95% CI)	p-value
HbA <sub>1c</sub> (%)	8.87	Liraglutide	263	6.99 (0.07)	-0.50 (-0.70, -0.30)	<0.0001
		Glibenclamide	130	7.50 (0.09)		
FPG (mmol/l)	11.26	Liraglutide	261	7.62 (0.11)	-0.72 (-1.01, -0.42)	<0.0001
		Glibenclamide	130	8.34 (0.14)		
Bodyweight (kg)	65.06	Liraglutide	265	64.06 (0.15)	-1.91 (-2.34, -1.48)	<0.0001
		Glibenclamide	130	65.97 (0.20)		
BNP (pg/ml)	19.25	Liraglutide	264	14.08 (1.76)	-10.71 (-15.76, -5.66)	<0.0001
		Glibenclamide	129	24.78 (2.33)		
PAI-1 (ng/ml)	30.74	Liraglutide	264	31.50 (1.14)	-2.89 (-6.18, 0.39)	0.0842
		Glibenclamide	129	34.40 (1.52)		
hsCRP (mg/dl)	0.1052	Liraglutide	264	0.0886 (0.0078)	-0.0226 (-0.0449, -0.0002)	0.0476
		Glibenclamide	129	0.1111 (0.0103)		

BNP: Brain natriuretic peptide; FPG: Fasting plasma glucose; HbA<sub>1c</sub>: Glycated hemoglobin; hsCRP: High-sensitivity C-reactive protein; LOCF: Last observation carried forward; LS: Least-squares; PAI: Plasminogen activator inhibitor; SE: Standard error.  
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most symptoms were transient and improved or resolved with observation [24].

Since liraglutide stimulates insulin secretion in a blood glucose-dependent manner, when used as a monotherapy, the incidence of hypoglycemia is very low [13]. However, when liraglutide has been used concomitantly with SU drugs, a higher incidence of hypoglycemia has been reported than that observed with liraglutide monotherapy. Consequently, caution is needed when combining liraglutide with SU drugs [14].

Although not reported in Japanese clinical studies, acute pancreatitis has been reported in overseas clinical studies. In patients with a history of pancreatitis, caution is necessary with liraglutide administration or liraglutide should be avoided. If persistent abdominal pain occurs, liraglutide should be discontinued and not reintroduced. A recent report demonstrated that sitagliptin, a DPP-4 inhibitor, and exenatide did not increase the risk of acute pancreatitis in T2DM patients [25]. The rates of other adverse reactions are shown in Table 5 [24].

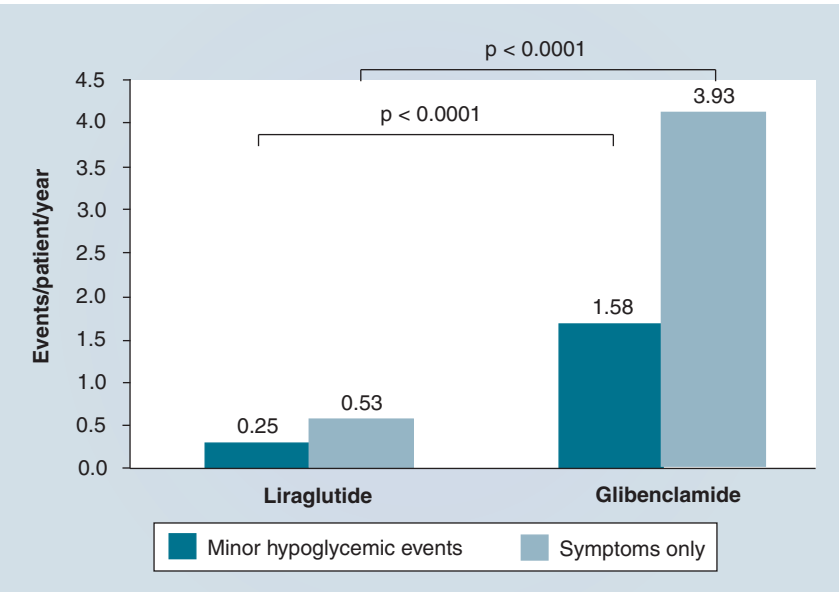


Figure 5. Hypoglycemic events in liraglutide monotherapy trial.  
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■ Drug interactions

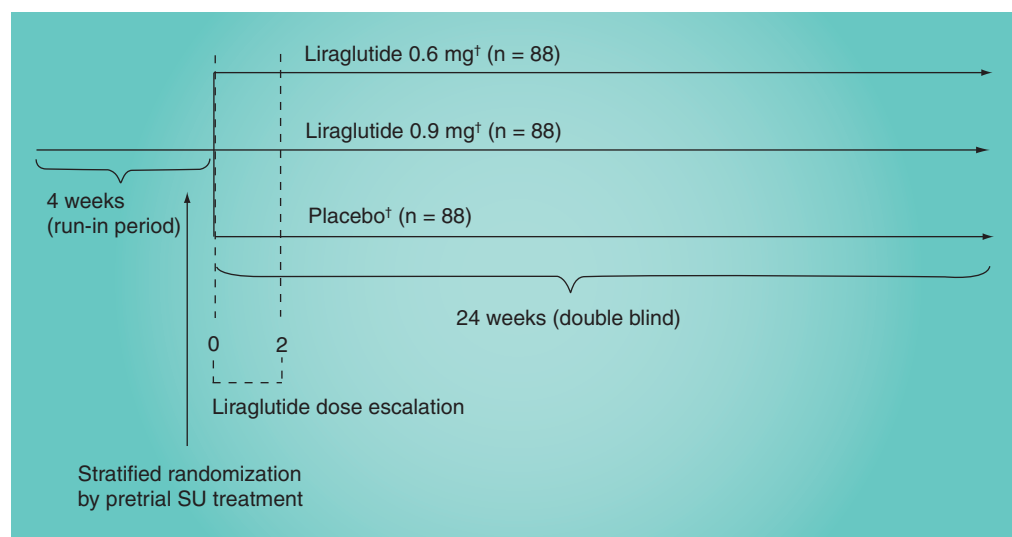
Increased hypoglycemia was reported with concomitant use of liraglutide with SU [14]. When liraglutide is used in combination with SU, dose reduction of the SU should be considered [24].

Increased hypoglycemia may occur when liraglutide is used with other antidiabetic agents. When hypoglycemic symptoms occur, SU should be temporarily discontinued or the dose reduced.

■ Use in specific populations

As mentioned in the ‘Pharmacokinetics’ section, after administering liraglutide to patients with renal or hepatic function impairment, there were no pharmacokinetic or pharmacodynamic events of particular concern. However, these observations were from single dose administration studies with a small number of patients. Caution is needed when administering liraglutide to T2DM patients with concomitant renal or hepatic function impairment. In the elderly also, no differences





**Figure 6. Liraglutide plus Sulfonylurea trial design (Phase III trial conducted in Japan).**

\*Patients continued pretrial SU treatment.

SU: Sulfonylurea.

Reproduced with permission from [14].

in pharmacokinetics or pharmacodynamics deserving special mention were observed. However, the risk of gastrointestinal symptoms and hypoglycemia is higher in the elderly. Therefore, liraglutide should be administered with care in this population, especially when used in combination with SUs.

The safety of liraglutide has not been established in pregnant women. Increased early embryonic death was observed in rats at doses corresponding to 21-times the maximum recommended human dose. Women who are pregnant or may be pregnant should not be treated with liraglutide. The transfer of liraglutide into milk was low in animal studies; caution should be exercised with liraglutide treatment in lactating women. The safety of liraglutide in pediatric patients has not been established.

## Conclusion

The efficacy and safety of liraglutide was studied in six randomized Liraglutide Effect and Action in Diabetes (LEAD) Phase III trials, completed in 2007 [26]. Of these, the LEAD-3 and -6 trials are ongoing with extension phases. The LEAD program included approximately 6500 subjects in 41 countries, of whom approximately 4445 received liraglutide. Liraglutide was investigated as monotherapy or in combination with different OADs, comparing it with SU drugs, glitazone, insulin glargine and exenatide. In the LEAD studies, liraglutide was associated with

significant reductions in HbA<sub>1c</sub>, ranging from 0.84 to 1.50% with liraglutide doses of 1.2 and 1.8 mg, respectively [27–32].

The dose–response study established the clinical dose of liraglutide in Japan as 0.9 mg/day, compared with 1.2 and 1.8 mg/day in other countries [12]. Patients in the Japanese clinical trials achieved greater HbA<sub>1c</sub> reductions than patients in Western countries, despite the lower liraglutide dose. In the Japanese monotherapy study, the HbA<sub>1c</sub> reduction from baseline was 1.74% with a liraglutide dose of 0.9 mg/day [13], and a combined use with a SU reduced HbA<sub>1c</sub> levels by 1.56% from baseline [14]. On the other hand, the HbA<sub>1c</sub> reduction from baseline was 0.84% with a liraglutide dose of 1.2 mg and 1.14% with liraglutide dose of 1.8 mg in the LEAD 3 monotherapy study [27]. These results strongly suggest that Japanese population is more sensitive to liraglutide treatment.

Interestingly, a 100 mg daily dose of sitagliptin was also more effective in HbA<sub>1c</sub> reduction in the studies conducted in Asian countries compared with those in Western countries [33–35]. These results suggest that Asian subjects, including Japanese people, are more sensitive to incretin-related drugs such as DPP-4 inhibitors and GLP-1 receptor agonists, although there were no direct comparisons between the two populations. To explain the ethnic difference on clinical efficacy, one can speculate that glycemic control

**Table 4. Metabolic parameters and cardiovascular biomarkers at 24 weeks in a liraglutide plus sulfonylurea trial.**

End point	Parameter	Liraglutide 0.6 mg/day	Liraglutide 0.9 mg/day	Placebo	p-value <sup>†</sup>
HbA <sub>1c</sub> (%)	Baseline, mean (SD)	8.60 (0.92)	8.23 (0.78)	8.45 (0.99)	<0.0001 <sup>‡</sup>
	Week 24 (LOCF) LS mean (SD)	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 HbA <sub>1c</sub> – baseline to week 24 (%)	Week 24 (LOCF) LS mean (SD)	-1.46 (0.95)	-1.56 (0.84)	-0.40 (0.93)	N/A
Mean seven-point SMPG profile (mmol/l)	Baseline, mean (SD)	11.75 (2.43)	11.05 (2.42)	10.91 (2.33)	<0.0001 <sup>‡</sup>
	Week 24 (LOCF) LS mean (SD)	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 (SD)	9.86 (2.26)	9.18 (2.07)	9.148 (2.36)	<0.0001 <sup>‡</sup>
	Week 24 (LOCF) LS mean (SD)	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 <sub>0–3h</sub> PG (mmol h/l)	Baseline, mean (SD)	44.27 (7.93)	41.73 (8.29)	41.77 (9.20)	<0.0001 <sup>‡</sup>
	Week 24 (LOCF) LS mean (SD)	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)	–	
Bodyweight (kg)	Baseline, mean (SD)	66.06 (12.19)	64.57 (12.03)	66.65 (13.49)	<0.0001 <sup>§</sup>
	Week 24 (LOCF) LS mean (SD)	66.12 (12.34)	64.20 (12.17)	65.53 (13.68)	
	Liraglutide – placebo, mean (95% CI)	1.18 (0.63, 1.73)	0.75 (0.21, 1.30)	–	
BNP (pg/ml)	Baseline, mean (SD)	20.71 (27.37)	19.03 (30.25)	17.85 (24.63)	0.0018 <sup>§</sup>
	Week 24 (LOCF) LS mean (SD)	14.67 (21.99)	15.13 (30.27)	20.47 (28.90)	
	Liraglutide – placebo, mean (95% CI)	-8.11 (-13.16, -3.06)	-6.24 (-11.28, -1.19)	–	
hsCRP (mg/dl)	Baseline, mean (SD)	0.1326 (0.1447)	0.0963 (0.1150)	0.1478 (0.1523)	0.0218 <sup>§</sup>
	Week 24 (LOCF) LS mean (SD)	0.0823 (0.0867)	0.0968 (0.1169)	0.1225 (0.1303)	
	Liraglutide – placebo, mean (95% CI)	-0.0338 (-0.0626, -0.0050)	-0.0035 (-0.0326, 0.0256)	–	
PAI-1 (ng/ml)	Baseline, mean (SD)	36.26 (20.60)	32.89 (23.22)	34.69 (20.59)	N/A
	Week 24 (LOCF) LS mean (SD)	34.31 (20.26)	32.95 (21.77)	32.79 (21.57)	
	Liraglutide – placebo, mean (95% CI)	0.77 (-4.51, 6.06)	1.11 (-4.18, 6.40)	–	

<sup>†</sup>Pairwise comparison.<sup>‡</sup>Both doses vs placebo.<sup>§</sup>0.6 mg/day + SU vs placebo.<sup>¶</sup>0.9 mg/day + SU vs placebo.<sup>§</sup>Overall comparison.AUC: Area under the curve; BNP: Brain natriuretic peptide; FPG: Fasting plasma glucose; HbA<sub>1c</sub>: Glycated hemoglobin; hsCRP: High-sensitivity C-reactive protein; LOCF: Last observation carried forward; LS: Least-squares; N/A: Not available; PAI: Plasminogen activator inhibitor; PG: Plasma glucose; SD: Standard deviation; SMPG: Self-monitored plasma glucose; SU: Sulfonylurea.

Data taken from [14].

in Asian subjects is much more dependent on a supplement of insulin secretion, rather than amelioration of insulin resistance.

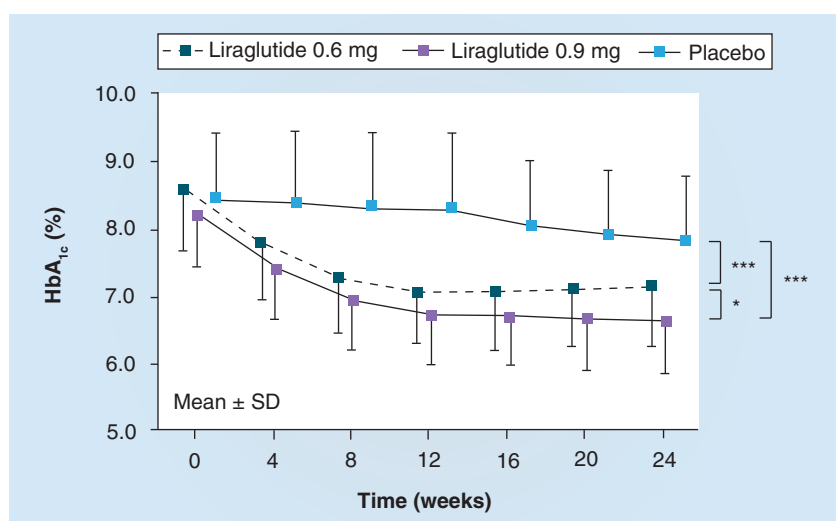
The incidence of gastrointestinal disturbances was lower in the Japanese studies than in the LEAD studies. Their rates of weight

reduction and blood pressure reduction were lower in the Japanese studies than in the LEAD studies.

Selection of an appropriate liraglutide dose for Japanese patients (0.9 mg/day) results in excellent lowering of blood glucose levels, while minimizing adverse effects such as gastrointestinal disturbances. When beginning liraglutide administration, SMBG should be performed in the initial stages to monitor for the occurrence of hyperglycemia or hypoglycemia. SMBG monitoring is recommended until the dose reaches the maintenance level and the blood glucose level has stabilized, especially when switching from other antidiabetic drugs or during concomitant SU therapy.

The addition of liraglutide to SU therapy is effective in patients with inadequate glycemic control on SU therapy alone [14]. When liraglutide is added to a SU, the SU dose should be reduced and the daily dose of liraglutide escalated cautiously at an interval of at least 1 week to avoid major hypoglycemic episodes. The reason for this is that shortly after sitagliptin was introduced in Japan, there were multiple cases of major hypoglycemia resulting from concomitant use with SU drugs.

On the other hand, acute hyperglycemia and diabetic ketoacidosis has been reported in patients who switched from insulin to liraglutide in Japan. Because the liraglutide dose titration method (initiated at 0.3 mg/day) requires a 2-week period to reach a 0.9 mg/day full dose, plasma glucose levels may increase for a while after switching from



**Figure 7. Glycated hemoglobin over time in a liraglutide plus sulfonylurea trial.**

\* $p < 0.05$ ; \*\*\* $p < 0.0001$ , p-values based on the analysis of variance model of  $HbA_{1c}$  at 24 weeks.

$HbA_{1c}$ : Glycated hemoglobin; SD: Standard deviation; SU: Sulfonylurea.

Data taken from [14].

insulin or a large dose of a SU drug. The use of liraglutide in insulin-dependent patients should be strictly avoided [36]. Liraglutide is not a substitute for insulin. The suitability of liraglutide for patients should be confirmed according to their insulin dependency before the drug is administered.

### Future perspective

The GLP-1 receptor agonist liraglutide has excellent efficacy and tolerability in Japanese patients with T2DM at doses of 0.9 mg/day,

**Table 5. Adverse events reported with liraglutide treatment.**

	Frequency		
	≥5%	1–5%	<1%
Hypersensitivity	–	–	Urticaria, pruritus
Hepatic	–	Increased AST, increased APT, abnormal hepatic function	–
Gastrointestinal	Constipation	Nausea, diarrhea, gastric discomfort, abdominal distension, reflux esophagitis	Upper abdominal pain, vomiting, dyspepsia, gastritis, decreased appetite, anorexia, gastroenteritis
Nervous system	–	Headache	Dizziness, hypoesthesia
Endocrine system	–	Thyroid nodule	–
Eyes	–	Diabetic retinopathy	–
Injection site	–	–	Erythema, rash
Respiratory	–	–	Cough
Cardiovascular	–	–	Ventricular extrasystoles, hypertension
Other	–	–	Chest pain, malaise

Data taken from [36].

with similar or superior effects than those observed in Western patients treated with liraglutide at 1.8 mg/day. However, the results of clinical trials in Japan demonstrated that the reduced daily dose of liraglutide was not always sufficient to suppress weight gain, especially in overweight patients. In addition, the current clinical practice of liraglutide is limited to monotherapy or combination with a SU drug in Japan. Therefore, further studies may be required to increase daily maximum dosage and extend the indication of combination therapy with other OADs in the future. Although the effects of long-term administration and some

other aspects of liraglutide are not yet known, it is expected that liraglutide will have a major role in the treatment of diabetes mellitus.

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# Bibliography

- 1 Fukushima M, Suzuki H, Seino Y. Insulin secretion capacity in the development from normal glucose tolerance to Type 2 diabetes. *Diabetes Res. Clin. Pract.* 66 (Suppl. 1), S37–S43 (2004).
- 2 Tripathy D, Carlsson M, Almgren P *et al.* Insulin secretion and insulin sensitivity in relation to glucose tolerance: lessons from the Botnia Study. *Diabetes* 49(6), 975–980 (2000).
- 3 UK Prospective Diabetes Study (UKPDS). Overview of 6 years' therapy of Type II diabetes: a progressive disease. *Diabetes* 44(11), 1249–1258 (1995).
- 4 Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC.  $\beta$ -cell deficit and increased  $\beta$ -cell apoptosis in humans with Type 2 diabetes. *Diabetes* 52(1), 102–110 (2003).
- 5 Sakuraba H, Mizukami H, Yagihashi N *et al.* Reduced  $\beta$ -cell mass and expression of oxidative stress-related DNA damage in the islet of Japanese Type II diabetic patients. *Diabetologia* 45(1), 85–96 (2002).
- 6 UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with Type 2 diabetes (UKPDS 34). *Lancet* 352(9139), 854–865 (1998).
- 7 Kahn SE, Haffner SM, Heise MA *et al.* Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N. Engl. J. Med.* 355(23), 2427–2443 (2006).
- 8 Zarich SW. Antidiabetic agents and cardiovascular risk in Type 2 diabetes. *Nat. Rev. Endocrinol.* 5, 500–506 (2009).
- 9 Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in Type 2 diabetes. *Lancet* 368(9548), 1696–1705 (2006).
- 10 Holst JJ. The physiology of glucagon-like peptide 1. *Physiol. Rev.* 87(4), 1409–1439 (2007).
- 11 Vilsboll T, Krarup T, Madsbad S, Holst JJ. Defective amplification of the late phase insulin response to glucose by GIP in obese Type II diabetic patients. *Diabetologia* 45(8), 1111–1119 (2002).
- 12 Seino Y, Rasmussen MF, Zdravkovic M, Kaku K. 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. *Diabetes Res. Clin. Pract.* 81(2), 161–168 (2008).
- 13 Seino Y, Rasmussen MF, Nishida T, Kaku K. 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.* 26(5), 1013–1022 (2010).
- 14 Kaku K, Rasmussen MF, Clauson P, Seino Y. 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.* 12(4), 341–347 (2010).
- 15 Blonde L, Russell-Jones D. The safety and efficacy of liraglutide with or without oral antidiabetic drug therapy in Type 2 diabetes: an overview of the LEAD 1–5 studies. *Diabetes Obes. Metab.* 11(Suppl. 3), 26–34 (2009).
- 16 Hojberg PV, Zander M, Vilsboll T *et al.* Near normalization of blood glucose improves the potentiating effect of GLP-1 on glucose-induced secretion in patients with Type 2 diabetes. *Diabetologia* 51(4), 632–640 (2008).
- 17 Chang AM, Jakobsen G, Sturis J *et al.* The GLP-1 derivative NN2211 restores  $\beta$ -cell sensitivity to glucose in Type 2 diabetic patients after a single dose. *Diabetes* 52(7), 1786–1791 (2003).
- 18 Agersø H, Jensen LB, Elbrønd B, Rolan P, Zdravkovic M. The pharmacokinetics, pharmacodynamics, safety and tolerability of NN2211, a new long-acting GLP-1 derivative, healthy men. *Diabetologia* 45(2), 195–202 (2002).
- 19 Kageyama S, Hirao K, Shimizu A *et al.* Tolerability, pharmacokinetics, and pharmacodynamics of liraglutide, long-acting human GLP-1 analogue –Phase I studies in Japanese healthy subjects and subjects with Type 2 diabetes. *Endocrinol. Diabetol.* 24(1), 95–104 (2007).
- 20 Damholt B, Golor G, Wierich W, Pedersen P, Ekblom M, Zdravkovic M. An open-label, parallel group study investigating the effects of age and gender on the pharmacokinetics of the once-daily glucagon-like peptide-1 analogue liraglutide. *J. Clin. Pharmacol.* 46(6), 635–641 (2006).
- 21 Flint A, Nazzari K, Jagielski P, Hindsberger C, Zdravkovic M. Influence of hepatic impairment on pharmacokinetics of the human GLP-1 analogue, liraglutide. *Br. J. Clin. Pharmacol.* 70(6), 807–814 (2010).
- 22 Jacobsen LV, Hindsberger C, Robson R, Zdravkovic M. Effect of renal impairment on the pharmacokinetics of the GLP-1 analogue liraglutide. *Br. J. Clin. Pharmacol.* 68(6), 898–905 (2009).
- 23 The Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus. Report of the Committee on the classification and diagnostic criteria of diabetes mellitus. *J. Diabetes Invest.* 1(5), 212–228 (2010).

- 24 Seino Y, Rasmussen MF, Nishida T, Kaku K. 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 Invest.* DOI: 10.1111/j.2040-1124.2011.00103.x (2011) (Epub ahead of print).
- 25 Garg R, Chen W, Pendergrass M: Acute Pancreatitis in Type 2 diabetes treated with exenatide or sitagliptin. *Diabetes Care* 33, 2349–2354 (2010).
- 26 Madsbad S. Liraglutide effect and action in diabetes (LEAD<sup>TM</sup>) trial. *Expert Rev. Endocrinol. Metab.* 4(2), 119–129 (2009).
- 27 Garber A, Henry R, Ratner R *et al.* Liraglutide versus glimepiride monotherapy for Type 2 diabetes (LEAD-3 Mono): a randomized, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet* 373(9662), 473–481 (2009).
- 28 Marre M, Shaw J, Brandle M *et al.* Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). *Diabetic Medicine* 26(3), 268–278 (2009).
- 29 Nauck M, Anders F, 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* 32(1), 84–90 (2009).
- 30 Zinman B, Gerich J, Buse JB *et al.* Efficacy and safety of the human glucagon-like peptide-1 in combination with metformin and thiazolidinedione in patients with Type 2 diabetes (LEAD-4 Met + TZD). *Diabetes Care* 32(7), 1224–1230 (2009).
- 31 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 randomized controlled trial. *Diabetologia* 52(10), 2046–2055 (2009).
- 32 Buse J, Rosenstock J, Sesti G *et al.* Liraglutide once a day versus exenatide twice a day for Type 2 diabetes: a 26-week randomized, parallel-group, multinational, open-label trial (LEAD-6). *Lancet* 374(9683), 39–47 (2009).
- 33 Mohan V, Yang W, Son HY *et al.* Efficacy and safety of sitagliptin in the treatment of patients with Type 2 diabetes in China, India, and Korea. *Diabetes Res. Clin. Pract.* 83(1), 106–116 (2009).
- 34 Nonaka K, Kakikawa T, Sato A *et al.* Efficacy and safety of sitagliptin monotherapy in Japanese patients with Type 2 diabetes. *Diabetes Res. Clin. Pract.* 79(2), 291–334 (2008).
- 35 Raz I, Hanefeld M, Xu L, Caria C, Williams-Herman D, Khatami H; Sitagliptin Study 023 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with Type 2 diabetes mellitus. *Diabetologia* 49(11), 2564–2571 (2006).
- 36 Victoza Hikachu 18 mg. Prescribing Information. Novo Nordisk Inc., Japan October 2010 (3rd Version).

#### ■ Websites

- 101 WHO. WHO Fact Sheet No. 312: Diabetes [www.who.int/mediacentre/factsheets/fs312en](http://www.who.int/mediacentre/factsheets/fs312en) (Accessed 2 July 2010)
- 102 National Institute of Health and Nutrition (Japan). Outline for the results of the National Health and Nutrition Survey Japan, 2007 [www.nih.go.jp/eiken/english/research/project\\_nhns.html](http://www.nih.go.jp/eiken/english/research/project_nhns.html) (Accessed 2 July 2010)