

Pharmacodynamics of the glucagon-like peptide-1 receptor agonist lixisenatide in Japanese and Caucasian patients with type 2 diabetes mellitus poorly controlled on sulphonylureas with/without metformin

Y. Seino¹, A. Takami², G. Boka³, E. Niemoeller⁴ & D. Raccah⁵ on behalf of the PDY6797 investigators

¹Kansai Electric Power Hospital, Osaka, Japan

²Sanofi K.K., Tokyo, Japan

³Sanofi, Chilly Mazarin, France

⁴Sanofi, Frankfurt, Germany

⁵University Hospital Sainte-Marguerite, Marseille, France

Aims: The PDY6797 study evaluated efficacy, safety and pharmacodynamics of lixisenatide in Japanese and Caucasian patients with type 2 diabetes mellitus (T2DM) insufficiently controlled with sulphonylureas with/without metformin.

Methods: This randomized, double-blind, placebo-controlled trial comprised a single-dose assessment of lixisenatide 5 and 10 µg, and a 5- to 6-week repeated dose-escalation assessment of lixisenatide 5 to 30 µg once (QD) or twice daily (BID). The primary endpoint was change in postprandial plasma glucose (PPG) area under the curve (AUC)_[0:29–4:30 h] after a standardized breakfast at the highest tolerated lixisenatide dose. Change from baseline in glycated haemoglobin (HbA1c), 2-h PPG and fasting plasma glucose (FPG) were assessed, as were adverse events.

Results: Change from baseline in PPG AUC_[0:29–4:30 h] with lixisenatide QD and BID was significantly greater than placebo ($p < 0.0001$ for all study populations), with particularly prominent effects in Japanese patients. Greater reductions in PPG AUC_[0:29–4:30 h] were seen with lixisenatide QD versus BID, while the totality of evidence suggested that the lixisenatide 20 µg dose was optimal. In the overall population, changes from baseline for 2-h PPG, HbA1c and FPG were significant with lixisenatide QD and BID versus placebo ($p < 0.01$ for all). Lixisenatide was well tolerated.

Conclusions: Lixisenatide significantly reduced PPG AUC_[0:29–4:30 h] versus placebo at the highest well-tolerated dose in patients with T2DM treated with sulphonylureas with/without metformin and had a good safety and tolerability profile. Japanese patients experienced particular benefits with lixisenatide in terms of reductions in PPG excursions.

Keywords: Caucasian, Japanese, lixisenatide, prandial, type 2 diabetes mellitus

Date submitted 5 November 2013; date of first decision 12 December 2013; date of final acceptance 6 February 2014

Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disorder that occurs as a result of insulin resistance and low levels of endogenous insulin production regardless of ethnicity. However, the characteristics of gluoregulation differ between Japanese and Caucasian individuals with or without T2DM. For example, Japanese persons reportedly have decreased early-phase insulin secretion, lower levels of β -cell function, a decreased reserve capacity of insulin secretion and increased insulin resistance compared with normative levels based on Caucasian

populations [1–3]. Furthermore, in Japanese populations, a high frequency of a number of polymorphisms in genes with roles in normal glucose homeostasis and energy expenditure has been reported, predisposing some individuals to obesity [4,5]. In spite of a metabolic background of low insulin secretion, the traditional Japanese lifestyle has historically had a protective effect against diabetes. However, the encroachment of sedentary work and a Western high-fat diet has increased insulin resistance in many Japanese individuals, which, in combination with predisposing genetic and metabolic factors, has resulted in a sudden upsurge in the prevalence of T2DM. Indeed, more than 13% of the Japanese population now has either T2DM or impaired glucose tolerance [6].

In individuals with normal glycaemic control, the release of insulin is amplified by the incretin hormones, limiting the extent of postprandial plasma glucose (PPG) excursions [7,8]. The incretin glucagon-like peptide-1 (GLP-1) is released postprandially by the intestine, leading to the release of insulin

Correspondence to: Yutaka Seino, MD, PhD, Kansai Electric Power Hospital, 2-1-7 Fukushima, Fukushima Ku, Osaka 553-0003, Japan.
E-mail: seino.yutaka@e2.kepcoco.jp

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

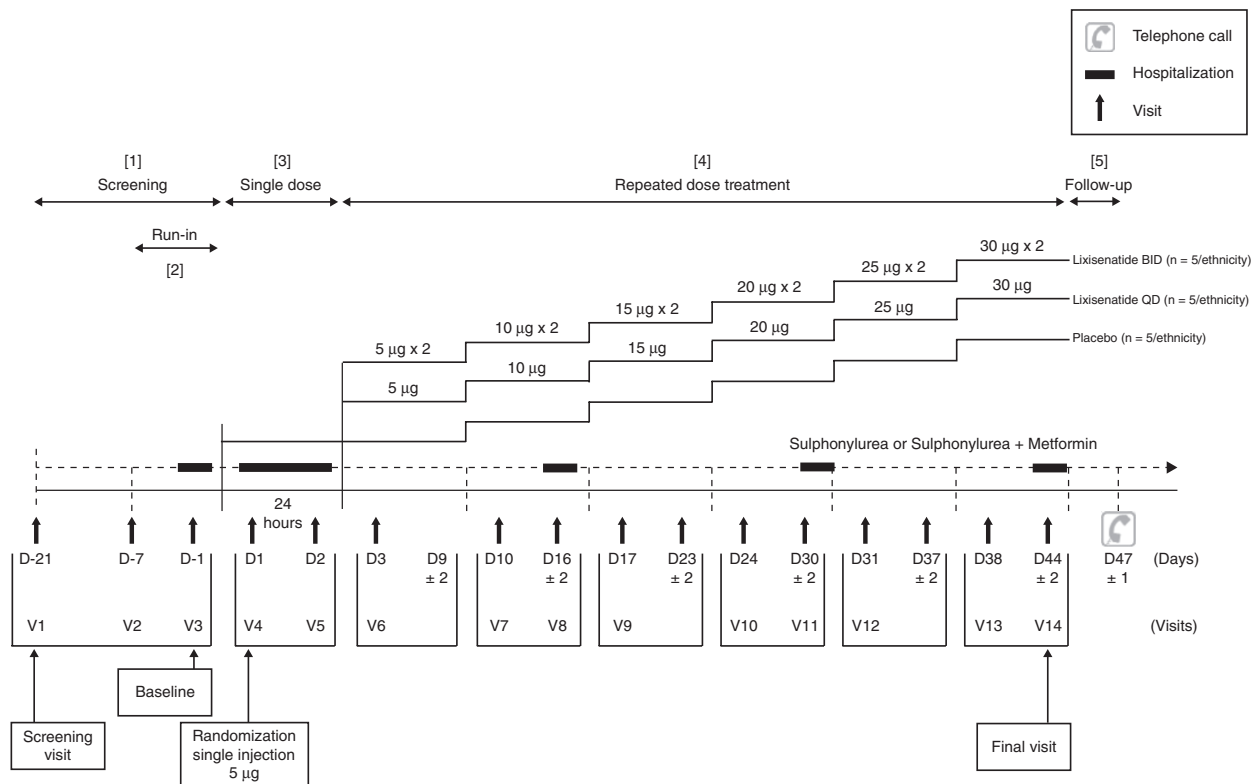


Figure 1. Trial design at the 5 µg starting dose for lixisenatide or volume-matched placebo in patient cohort 1. Patients in cohort 2 received a single injection of lixisenatide 10 µg at randomization. Patients in cohort 2 started treatment with the 10 µg dose and then followed the same dose increase regimen, meaning that they received treatment for 1 week less than patients in cohort 1.

and the suppression of glucagon release. Native GLP-1 is rapidly inactivated by dipeptidyl peptidase-4 (DPP-4) [9]. Endogenous GLP-1 levels are low in healthy Japanese subjects and in Japanese patients with T2DM; furthermore, meal-induced secretion of GLP-1 is considered to be negligible in both of these groups [10–12].

Early T2DM can generally be controlled with lifestyle measures and the use of oral antidiabetic drugs (OADs) [13,14]. Sulphonylureas have historically been, and continue to be, the most commonly used OAD in Japan; however, use of other OADs, including the biguanide metformin, is growing [15]. T2DM is a chronic disease and increasing insulin resistance and declining β-cell function may mean that add-on medication to OADs is required to maintain effective glycaemic control.

Lixisenatide (Lyxumia®; Sanofi, Paris, France) is a once-daily (QD) prandial GLP-1 receptor agonist (RA) for the treatment of T2DM. Lixisenatide is structurally similar to the GLP-1 RA exenatide and both are structurally related to, but distinct from, GLP-1 and withstand degradation by DPP-4, thus prolonging their activity at GLP-1 receptors [16]. Compared with exenatide, lixisenatide has a modified C terminus. This trial evaluated the pharmacodynamics of lixisenatide in Japanese and Caucasian patients with T2DM poorly controlled on sulphonylureas with or without metformin in order to provide data pertaining to potential effects of ethnicity, and also efficacy and safety data with dose escalation. A stepwise dose initiation with lixisenatide was further evaluated in the phase

III clinical programme in order to minimize gastrointestinal adverse events (AEs), which are a class effect with GLP-1 RAs. The effects of GLP-1 RAs as monotherapies or in combination with insulin or OADs in Asian patients and, more specifically, Japanese patients have been investigated previously [17–27]. However, the possibility that low endogenous GLP-1 production in Japanese patients results in differential effects with GLP-1 RA treatment compared with effects in Caucasian patients is intriguing and a direct comparison trial has not been reported previously.

The PDY6797 trial comprised a single-dose assessment of lixisenatide 5 and 10 µg, and a 5- to 6-week repeated dose-escalation assessment of lixisenatide once (QD) or twice daily (BID) following dose increases from 5 to 30 µg. In both sets of assessments, the effect of lixisenatide was monitored on PPG excursions after a standardized breakfast.

Materials and Methods

Trial Design

This was an international, multicentre, randomized, double-blind, placebo-controlled, combined single-dose and repeated dose-escalation, parallel-group trial conducted in Japanese and Caucasian patients. The trial was conducted at 30 centres in five countries (Australia, Germany, Japan, South Africa and the Netherlands). The trial comprised five periods (Figure 1): (i) an up to 2-week screening phase; (ii) a single-blind placebo

run-in period of 1 week with volume-matched placebo for lixisenatide 5 µg BID (i.e. one injection in the morning before breakfast and one injection in the evening before dinner); (iii) a single-dose period with randomization on the first day of dosing with a single injection in the morning (lixisenatide 5 µg or volume-matched placebo in cohort 1 and lixisenatide 10 µg or volume-matched placebo in cohort 2), followed by a placebo injection observation period of 2 days; (iv) a double-blind, placebo-controlled, dose-escalation, parallel-group period of 5 or 6 weeks of repeated-dose treatment administered QD or BID (according to starting dose: i.e. lixisenatide 10 µg per injection or volume-matched placebo, or 5 µg per injection or volume-matched placebo); and (v) a posttreatment follow-up period of 72 ± 24 h.

All patients signed an informed consent form. The protocol for this trial complied with the recommendations of the Declaration of Helsinki and was submitted to and approved by independent ethics committees and/or the institutional review boards for each of the participating centres.

Patients were centrally randomized by an interactive voice response system in a 1 : 1 : 1 ratio to receive lixisenatide BID, lixisenatide QD or matching placebo within each ethnicity. The trial was double-blind with regard to QD/BID regimen and active versus placebo treatment but was not blinded with regard to trial drug volume. A central laboratory was used for the analysis of efficacy and safety parameters in this study (BARC, Ghent, Belgium) and an independent Data Monitoring Committee supervised the conduct of the study. Possible allergic events were adjudicated in a blinded manner by an external Allergic Reaction Assessment Committee (ARAC).

Study Population. Included patients were Japanese or Caucasian men and postmenopausal women aged 20–75 years at screening with T2DM for at least 1 year prior to screening diagnosed according to American Diabetes Association criteria [28]. All included patients had glycated haemoglobin (HbA1c) ≥7.0 and ≤10.0% at the time of screening. Japanese patients living outside Japan were required to have Japanese nationality, both parents Japanese, and have not lived outside Japan for >5 years. Treatment with sulphonylurea with/without metformin was required to be at a stable dose for at least 3 months prior to screening. At the time of screening, included patients had a body mass index (BMI) ≤35 kg/m² at screening and fasting plasma glucose (FPG) between 108 and 250 mg/dl (6.0–13.9 mmol/l).

The main exclusion criteria were use of OADs other than a sulphonylurea or metformin within 3 months prior to screening or use of insulin for ≥1 week within the 6 months before screening. Other exclusion criteria included a history of chronic pancreatitis, pancreatectomy, stomach/gastric surgery, inflammatory bowel disease or irritable bowel syndrome, or a clinically relevant history of gastrointestinal disease associated with prolonged nausea and vomiting, including gastroparesis, within 6 months prior to the time of screening.

Interventions. Lixisenatide or volume-matched placebo were self-administered subcutaneously in the thigh, abdomen or upper arm using a pen-type injector (OptiClik®, Sanofi). During the single-dose assessment, patients were administered

the investigational drug (lixisenatide or volume-matched placebo) 5 µg (cohort 1) or 10 µg (cohort 2) exactly 30 min before the standardized meal. In the repeated dose-escalation assessment, patients in cohort 1 administered a starting dose of 5 µg QD or BID increasing every week in 5 µg increments – provided safety and tolerability did not prevent further dose increase – up to a total of 30 µg daily in the QD group and 60 µg daily in the BID group for 6 weeks. Patients in cohort 2 started with a dose of 10 µg QD or BID and then followed the same dose increase regimen described for cohort 1. Patients receiving lixisenatide QD administered lixisenatide in the morning and placebo in the evening; patients receiving lixisenatide BID administered lixisenatide in the morning and evening. Patients continued their previous dosage of sulphonylurea with/without metformin at a stable dose throughout the trial.

Efficacy and Safety Assessments. The primary endpoint of this trial was change from baseline in PPG area under the curve (AUC)_[0:29–4:30 h] (h · mg/dl) after a standardized breakfast on the last day at the highest well-tolerated dose. This parameter was considered to be appropriate in light of the 5- or 6-week study duration, the available evidence with lixisenatide and the mechanism of action of GLP-1 RAs. Ingredients of the standardized 500 kcal breakfast were orange juice (180 ml), toasted bread (60 g), jam or preserves (20 g), butter or margarine (10 g), whole milk (120 ml), and coffee or tea with non-nutritive sweetener if desired [29].

Secondary endpoints included the treatment by ethnicity interaction of increasing QD/BID doses of lixisenatide on PPG AUC_[0:29–4:30 h] (h · mg/dl) after a standardized breakfast in Japanese and Caucasian patients and change from baseline in PPG AUC_[0:29–4:30 h] and 2-h PPG (mg/dl) after a standardized breakfast on the last day of lixisenatide 10, 20 and 30 µg doses or on the last day at the highest well-tolerated dose. Additional secondary endpoints were: change from baseline in FPG (mg/dl), HbA1c (%) and body weight on the last day of treatment at the highest well-tolerated dose.

AEs were monitored, including injection-site reactions, vital signs (blood pressure and heart rate), 12-lead electrocardiograms, laboratory tests (haematology and serum chemistry), symptomatic hypoglycaemia and severe hypoglycaemia. Symptomatic hypoglycaemia was defined as symptoms consistent with hypoglycaemia with an accompanying blood glucose <60 mg/dl (3.3 mmol/l) or symptoms of hypoglycaemia without an accompanying blood glucose measurement, as long as the event was associated with prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration. Severe hypoglycaemia was defined as an event with clinical symptoms that were considered to result from hypoglycaemia during which the patient required the assistance of another person and the event was associated with blood glucose <36 mg/dl (<2.0 mmol/l) or, if no blood or plasma glucose measurement was available, the event was associated with prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration.

Trial Populations. The modified intent-to-treat (mITT) population included all randomized patients who took at least one

dose of trial medication and had a baseline and at least one postbaseline on-treatment value for the efficacy variables. The per-protocol (PP) population was defined as a subset of the mITT population who were treated at the 20 µg dose level or above on the last day of week 6 for cohort 1 or on the last day of week 5 for cohort 2, respectively; had a primary efficacy value at this dose level; and had no major protocol deviations. The safety population was defined as all randomized patients who took at least one dose of trial medication.

Statistical Methods

Sample Size Determination. The primary analysis was based on the PP population. Assuming 20% of patients would have a major protocol deviation, including early withdrawal, and a two-sided *t*-test of the null hypothesis of no treatment difference and a type one error rate of 5%, 20 patients randomized in each treatment group for each ethnicity would provide 90% power to detect a difference of change from baseline in PPG AUC_[0:29–4:30 h] (h · mg/dl) of -300 h · mg/dl (after a standardized breakfast) on the last day of the highest well-tolerated dose between each lixisenatide arm and placebo with the common standard error (s.e.) 250 h · mg/dl.

Statistical Analysis. The primary efficacy variable was analysed using an analysis of covariance (ANCOVA) model with treatment, cohort, ethnicity and interaction of treatment-by-ethnicity as fixed factors, and using baseline value as a covariate based on the PP population. An additional sensitivity analysis was also performed on the mITT population. The potential treatment-by-ethnicity interaction (performed on the mITT population) and other secondary variables were also tested using this ANCOVA model. Adjusted means, 95% confidence intervals (CIs) for adjusted means and *p*-values (if appropriate) for comparison of lixisenatide QD or BID versus placebo were obtained overall and also by ethnicity. No adjustment for multiplicity was implemented. All safety data were summarized by treatment and ethnicity.

Results

The first patient was enrolled in this trial on 3 November 2006 and the last patient completed the trial on 16 September 2007. Patient disposition is shown in Figure S1, Supporting information. In total, 120 patients were randomized in this trial. A total of 117 patients completed the study with 1 patient discontinuing in the placebo arm and 2 patients discontinuing in the lixisenatide BID arm (all due to AEs). The safety population comprised 120 patients, the mITT population comprised 119 patients and the PP population comprised 110 patients (lixisenatide QD *n* = 34, lixisenatide BID *n* = 37 and placebo *n* = 39).

Baseline Data

Table 1 shows baseline demographics and clinical characteristics for the overall population and for the population by ethnicity. Age, sex and duration of diabetes were similar across treatment groups and the median patient age was

62.0 years; 78.3% of patients were male. Compared with Caucasian patients, Japanese patients were more likely to be treated with sulphonylureas without metformin, had a shorter duration of sulphonylurea and metformin use, and were treated with lower daily doses of sulphonylureas or metformin.

Mean PPG AUC_[0:29–4:30 h] at baseline ranged from 781.8 to 902.6 h · mg/dl (Table 1). Baseline FPG and PPG after breakfast were well balanced between Caucasian and Japanese patients (Table 2). Compared with Caucasian patients at baseline, Japanese patients were more likely to have HbA1c $\geq 8.5\%$ (Table 1), have higher HbA1c (Table 2), lower body weight (Table 2) and a lower BMI (Table 1).

Differences between the lixisenatide QD and BID groups at baseline included younger age, higher rates of sulphonylurea plus metformin use, longer T2DM duration and longer duration of sulphonylurea use in the lixisenatide QD group (Table 1). Patients treated with lixisenatide BID were more likely to be treated with a sulphonylurea without metformin (Table 1), had higher HbA1c at baseline (Table 2) and were of greater body weight (Table 2).

Primary Endpoint

In the PP population, least square (LS) mean (s.e.) differences in PPG AUC_[0:29–4:30 h] were -333.4 (26.9) and -288.8 (26.1) h · mg/dl for lixisenatide QD and BID versus placebo, respectively (*p* < 0.0001 for both; Figure 2). The LS mean (s.e.) difference in PPG AUC_[0:29–4:30 h] for Japanese patients was -406.7 (36.7) and -346.3 (35.1) h · mg/dl for lixisenatide QD and BID versus placebo, respectively (*p* < 0.0001 for both; Figure 2) and for Caucasian patients it was -260.1 (39.5) and -231.3 (38.6) h · mg/dl for lixisenatide QD and BID versus placebo, respectively (*p* < 0.0001 for both; Figure 2).

Secondary Endpoints

The LS mean difference between lixisenatide QD/BID combined and placebo for the primary endpoint of change from baseline versus placebo in PPG AUC_[0:29–4:30 h] in Japanese versus Caucasian patients in the mITT population was -122.3 h · mg/dl (95% CI: -211.10 , -33.51 ; *p* = 0.0074). These data indicated that, compared with Caucasian patients, Japanese patients treated with lixisenatide experienced a significantly greater benefit in terms of reduction of PPG AUC_[0:29–4:30 h] after a standardized breakfast.

Reductions in PPG AUC_[0:29–4:30 h] after the standardized breakfast were observed with lixisenatide QD and BID versus placebo in both ethnic groups at all doses, with a greater effect reported in Japanese patients (Figure 3). In Japanese patients, maximum PPG AUC_[0:29–4:30 h] reductions were achieved with the lixisenatide 20 µg QD dose, while Caucasian patients experienced similar reductions at both the 20 and 30 µg doses (QD or BID), which were both greater than that for the 10 µg dose.

LS mean (s.e.) change from baseline in the secondary efficacy parameters for each treatment group is shown in Table 2. The LS mean (s.e.) differences in 2-h PPG after a standardized breakfast in patients treated with lixisenatide QD and BID versus placebo in the overall population at the highest well-tolerated dose were -124.9 (10.0) and -103.4 (9.8) mg/dl,

Table 1. Baseline demographic data and clinical characteristics overall and by ethnicity – safety population.

Parameters	Overall population			Japanese patients			Caucasian patients		
	Lixisenatide QD (n = 39)	Lixisenatide BID (n = 41)	Placebo (n = 40)	Lixisenatide QD (n = 20)	Lixisenatide BID (n = 22)	Placebo (n = 21)	Lixisenatide QD (n = 19)	Lixisenatide BID (n = 19)	Placebo (n = 19)
Median age, years (min, max)	62.0 (44.0, 74.0)	64.0 (47.0, 75.0)	62.5 (36.0, 73.0)	62.0 (47.0, 74.0)	63.5 (47.0, 74.0)	64.0 (36.0, 73.0)	61.0 (44.0, 74.0)	66.0 (47.0, 75.0)	62.0 (39.0, 71.0)
Male gender, n (%)	28 (71.8)	32 (78.0)	34 (85.0)	14 (70.0)	17 (77.3)	16 (76.2)	14 (73.7)	15 (78.9)	18 (94.7)
Mean (s.d.) BMI, kg/m ²	25.1 (3.7)	27.5 (4.4)	26.4 (3.5)	22.6 (2.2)	25.9 (4.4)	24.5 (3.2)	27.8 (2.8)	29.4 (3.5)	28.5 (2.6)
Prior OAD use, n (%)	14 (35.9)	19 (46.3)	18 (45.0)	12 (60.0)	16 (72.7)	15 (71.4)	2 (10.5)	3 (15.8)	3 (15.8)
Sulphonylurea*	25 (64.1)	22 (53.7)	22 (55.0)	8 (40.0)	6 (27.3)	6 (28.6)	17 (89.5)	16 (84.2)	16 (84.2)
+ metformin	10.4 (2.5, 26.8)	7.4 (1.2, 45.3)	8.4 (1.4, 21.4)	10.8 (2.9, 26.8)	5.7 (1.4, 40.3)	8.0 (1.5, 15.0)	10.4 (2.5, 20.0)	10.1 (1.2, 45.3)	8.4 (1.4, 21.4)
Median (min, max) duration of T2DM, years	2.6 (0.4, 16.4)	4.3 (0.3, 45.3)	1.8 (0.3, 17.3)	1.9 (0.4, 6.1)	1.6 (0.3, 5.9)	0.7 (0.3, 3.0)	7.4 (0.5, 16.4)	6.9 (0.3, 45.3)	2.8 (0.3, 17.3)
Mean (s.d.) metformin total daily dose, g/day	1.4 (0.9)	1.6 (1.0)	1.3 (0.7)	0.6 (0.2)	0.5 (0.2)	0.5 (0.2)	1.8 (0.8)	2.0 (0.8)	1.6 (0.6)
Median (min, max) duration of sulphonylurea use, years	2.1 (0.3, 16.4)	1.8 (0.3, 18.1)	1.5 (0.3, 17.3)	1.2 (0.3, 5.0)	0.9 (0.3, 5.9)	1.3 (0.3, 8.7)	7.4 (0.4, 16.4)	5.3 (0.8, 18.1)	2.7 (0.4, 17.3)
Mean (s.d.) baseline PPG AUC _(0:29–4:30 h) (h · mg/dl)†	837.0 (153.8)	866.7 (169.6)	885.9 (164.8)	889.4 (150.8)	859.9 (189.4)	871.6 (156.3)	781.8 (140.2)	874.7 (148.0)	902.6 (177.2)
HbA1c group, n/N (%)	26 (66.7)	20 (48.8)	23 (57.5)	9 (45.0)	9 (40.9)	9 (42.9)	17 (89.5)	11 (57.9)	14 (73.7)
<8.5	13 (33.3)	21 (51.2)	17 (42.5)	11 (55.0)	13 (59.1)	12 (57.1)	2 (10.5)	8 (42.1)	5 (26.3)

AUC, area under the curve; BID, twice daily; BMI, body mass index; HbA1c, glycated haemoglobin; OAD, oral antidiabetic drug; PPG, postprandial plasma glucose; QD, once daily; s.d., standard deviation; T2DM, type 2 diabetes mellitus.

*Sulphonylureas used included glibenclamide, glibomet, gliclazide glimepiride, glipizide and tolbutamide.

†After a standardized breakfast.

Table 2. Baseline means and LS mean change from baseline for efficacy parameters on the last day at the highest well-tolerated dose in the overall population and by ethnicity – PP population.

Parameters	Overall population			Japanese patients			Caucasian patients		
	Lixisenatide QD (n = 34)	Lixisenatide BID (n = 37)	Placebo (n = 39)	Lixisenatide QD (n = 17)	Lixisenatide BID (n = 20)	Placebo (n = 21)	Lixisenatide QD (n = 17)	Lixisenatide BID (n = 17)	Placebo (n = 18)
2-h PPG* (mg/dl)									
Baseline mean (s.d.)	238.9 (52.4)	244.4 (58.9)	254.5 (50.9)	257.3 (56.1)	240.4 (67.4)	254.7 (51.1)	220.6 (42.4)	249.2 (48.6)	254.2 (52.1)
LS mean change (s.e.)	-150.2 (7.7)***	-128.7 (7.4)***	-25.3 (7.3)	-160.3 (10.8)	-141.4 (9.8)	-20.6 (9.6)	-140.1 (10.6)	-116.0 (10.6)	-30.0 (10.3)
FPG (mg/dl)									
Baseline mean (s.d.)	163.0 (30.7)	169.2 (39.4)	165.3 (40.3)	154.3 (25.3)	167.1 (31.5)	147.6 (33.1)	171.6 (33.8)	171.8 (48.0)	185.9 (38.8)
LS mean change (s.e.)	-33.9 (4.4)**	-42.1 (4.3)***	-15.3 (4.2)	-41.1 (6.2)	-49.8 (5.6)	-18.7 (5.6)	-26.8 (6.1)	-34.4 (6.1)	-11.8 (6.1)
HbA1c (%)									
Baseline mean (s.d.)	8.17 (0.75)	8.49 (0.85)	8.39 (0.75)	8.59 (0.70)	8.64 (0.88)	8.64 (0.76)	7.75 (0.54)	8.32 (0.81)	8.11 (0.65)
LS mean change (s.e.)	-0.94 (0.07)***	-1.13 (0.07)***	-0.41 (0.07)	-1.13 (0.10)	-1.26 (0.09)	-0.37 (0.09)	-0.75 (0.10)	-1.00 (0.10)	-0.44 (0.10)
Body weight (kg)									
Baseline mean (s.d.)	72.51 (17.37)	79.06 (16.89)	76.29 (15.78)	60.51 (7.59)	71.71 (14.90)	66.76 (12.65)	84.51 (16.09)	87.71 (15.20)	87.41 (11.20)
LS mean change (s.e.)	-0.95 (0.33)	-0.85 (0.32)	-0.36 (0.31)	-0.70 (0.50)	-0.72 (0.42)	-1.06 (0.42)	-1.20 (0.46)	-0.98 (0.48)	0.34 (0.46)

** p < 0.01 versus placebo; *** p ≤ 0.001 versus placebo (p-values only provided for the overall population). BID, twice daily; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; LS, least squares; PP, per protocol; PPG, postprandial plasma glucose; QD, once daily; s.d., standard deviation; s.e., standard error.

*After a standardized breakfast

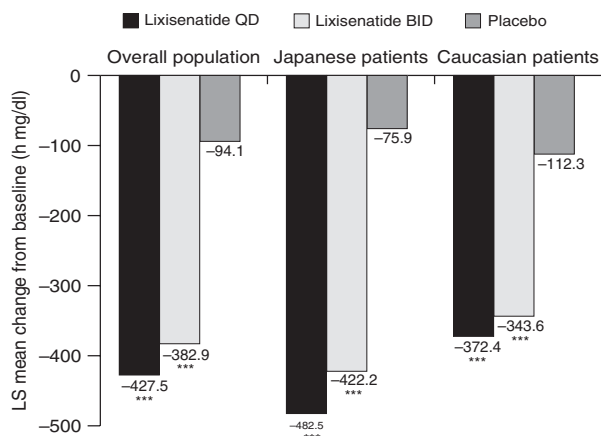


Figure 2. Least square (LS) mean change from baseline to trial end in postprandial plasma glucose (PPG) area under the curve (AUC)_[0:29–4:30 h] (h · mg/dl) at the highest well-tolerated dose of lixisenatide or placebo after a standardized breakfast in the overall population and by ethnicity – per protocol (PP) population. *** p < 0.0001 versus placebo. BID, twice daily; QD, once daily.

respectively (p < 0.0001 for both). In Japanese patients, LS mean differences (95% CI) in 2-h PPG with lixisenatide QD and BID versus placebo were -139.7 (-167.14, -112.31) and -120.8 (-147.12, -94.47) mg/dl, and in Caucasian patients were -110.0 (-138.93, -81.15) and -86.0 (-114.43, -57.63) mg/dl, respectively. Reductions in 2-h PPG were greatest at the 20 µg dose (for both lixisenatide QD and BID) in Japanese patients, while in Caucasian patients, reduction with lixisenatide QD and BID 20 and 30 µg doses were similar and were greater than that for the 10 µg dose (data not shown).

In the overall population, change from baseline in FPG on the last day of the highest well-tolerated dose was significantly greater with lixisenatide QD and BID compared with placebo [LS mean (s.e.) difference -18.6 (5.8) and -26.8 (5.6) mg/dl,

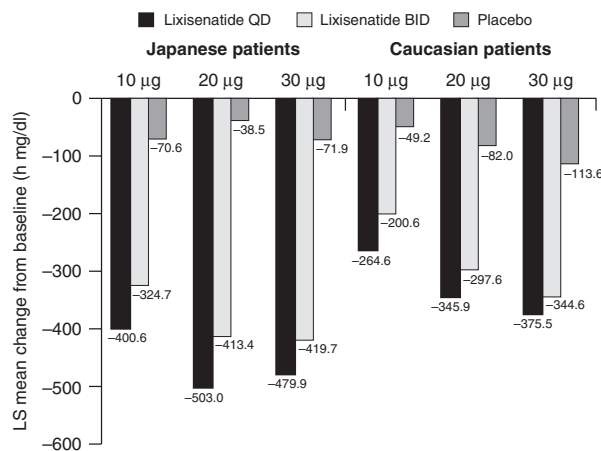


Figure 3. Least squares (LS) mean change from baseline in postprandial plasma glucose (PPG) area under the curve (AUC)_[0:29–4:30 h] (h · mg/dl) after a standardized breakfast on the last day of administration of lixisenatide 10, 20 and 30 µg or placebo by ethnicity – per protocol (PP) population. BID, twice daily; QD, once daily.

respectively; p < 0.01 for both]. The LS mean differences (95% CI) versus placebo in terms of FPG reductions from baseline for Japanese patients treated with lixisenatide QD or BID were -22.3 (-38.20, -6.47) and -31.1 (-46.43, -15.68) mg/dl and for Caucasian patients were -14.9 (-31.47, 1.57) and -22.6 (-39.06, -6.04) mg/dl, respectively.

In the overall population, the LS mean (s.e.) differences in change from baseline in HbA1c at the last day of the highest well-tolerated dose of lixisenatide QD and BID compared with placebo were -0.53% (0.09%) and -0.72% (0.09%), respectively (p < 0.0001 for both). LS mean differences (95% CI) in HbA1c change from baseline in Japanese patients treated with lixisenatide QD and BID versus placebo were -0.76% (-1.012, -0.505) and -0.89% (-1.133, -0.648), respectively. In Caucasian patients, LS mean differences (95% CI) versus

Table 3. Summary of TEAEs in the overall population and by ethnicity – safety population.

Parameter, n (%)	Overall population			Japanese patients			Caucasian patients		
	Lixisenatide QD (n = 39)	Lixisenatide BID (n = 41)	Placebo (n = 40)	Lixisenatide QD (n = 20)	Lixisenatide BID (n = 22)	Placebo (n = 21)	Lixisenatide QD (n = 19)	Lixisenatide BID (n = 19)	Placebo (n = 19)
Any TEAE	35 (89.7)	31 (75.6)	29 (72.5)	17 (85.0)	17 (77.3)	13 (61.9)	18 (94.7)	14 (73.7)	16 (84.2)
Any serious TEAE	0	1 (2.4)	1 (2.5)	0	0	0	0	1 (5.3)	1 (5.3)
TEAE leading to treatment discontinuation	0	2 (4.9)	1 (2.5)	0	1 (4.5)	0	0	1 (5.3)	1 (5.3)
Diarrhoea	3 (7.7)	9 (22.0)	5 (12.5)	1 (5.0)	5 (22.7)	1 (4.8)	2 (10.5)	4 (21.1)	4 (21.1)
Nausea	16 (41.0)	8 (19.5)	1 (2.5)	10 (50.0)	4 (18.2)	0	6 (31.6)	4 (21.1)	1 (5.3)
Vomiting	5 (12.8)	6 (14.6)	0	2 (10.0)	4 (18.2)	0	3 (15.8)	2 (10.5)	0
Symptomatic hypoglycaemia (according to prespecified per-protocol definition)	8 (20.5)	9 (22.0)	3 (7.5)	4 (20.0)	7 (31.8)	3 (14.3)	4 (21.1)	2 (10.5)	0

EU Clinical Trials Register Number: EUCTR2006-003138-13-DE. BID, twice daily; QD, once daily; TEAE, treatment-emergent adverse event.

placebo for HbA1c with lixisenatide QD and BID were -0.31% ($-0.573, -0.043$) and -0.56% ($-0.820, -0.293$), respectively.

In the overall population, weight change from baseline to the last day of the highest well-tolerated dose did not reach statistical significance [LS mean (s.e.) difference -0.59 (0.43) and -0.49 (0.42) kg versus placebo for the lixisenatide QD- and BID-treated patients, respectively]. Weight loss with lixisenatide treatment versus placebo was observed in Caucasian patients [LS mean differences (95% CI) -1.54 ($-2.749, -0.330$) and -1.32 ($-2.526, -0.111$) kg for lixisenatide QD and BID, respectively]. In Japanese patients, the LS mean differences (95% CI) with lixisenatide QD and BID versus placebo were 0.36 ($-0.819, 1.534$) and 0.34 ($-0.787, 1.458$) kg, respectively. A large placebo effect on body weight loss was observed in Japanese patients [LS mean (s.e.) change from baseline -1.06 (0.42) kg; Table 2].

Safety

Mean treatment duration of the trial ranged from 36.8 to 38.8 days. At study end, the majority (85–95%) of patients of either ethnicity were receiving ≥ 20 μ g lixisenatide.

Table 3 summarizes the occurrence of treatment-emergent adverse events (TEAEs). Table S1 summarizes TEAEs that occurred in $\geq 5\%$ of patients by organ system. Overall, the proportion of patients with TEAEs was similar among the three treatment groups, although the rate of TEAEs was slightly higher in the lixisenatide QD group. The patterns of AEs overall was similar in Japanese and Caucasian patients and no deaths were reported. Two serious AEs occurred, both in Caucasian patients; these were a new onset of second degree atrioventricular block and a case of coronary artery disease and neither event was judged to be related to treatment.

The TEAEs reported most frequently in the lixisenatide-treated patients were gastrointestinal disorders, particularly nausea, vomiting and diarrhoea, which had a similar distribution in both ethnicities; nausea and vomiting were more common in the active-treatment groups compared with placebo (Table 3). No patient permanently discontinued the study due

to these TEAEs, which were mostly mild to moderate in intensity. Higher rates of diarrhoea were reported in patients treated with lixisenatide BID compared with lixisenatide QD (Table 3).

In Japanese patients, four (20.0%), seven (31.8%) and three (14.3%) patients experienced predefined symptomatic hypoglycaemia in the lixisenatide QD and BID groups and the placebo group, respectively. The corresponding figures in Caucasian patients were, four (21.1%), two (10.5%) and zero patients, respectively (Table 3). No severe hypoglycaemic events occurred in this trial. No events of pancreatitis were reported. One event of application-site erythema was reported for a Japanese patient (placebo-treatment arm) and injection-site pain and injection-site reaction were reported once in a Caucasian patient (lixisenatide QD-treatment arm). One Japanese patient in the lixisenatide QD-treatment arm experienced allergic rhinitis adjudicated by the ARAC to be unrelated to study treatment.

Discussion

Treatment with lixisenatide over 5–6 weeks significantly improved PPG control in Japanese and Caucasian patients, as assessed by PPG AUC_[0:29–4:30 h] after a standardized breakfast on the last day at the highest well-tolerated dose. Overall, and for both ethnicities, there was a numerical trend towards a greater treatment effect with lixisenatide QD compared with lixisenatide BID. In addition, in the Japanese population, the maximum treatment effect was observed for the 20 μ g dose, while both the 20 μ g and the 30 μ g doses produced similar responses in Caucasian patients, suggesting that the 20 μ g dose is optimal.

The effect of other GLP-1 RAs in Asian patients with T2DM (including some Japanese patient-specific trials) has been reported previously [17–27]; however, herein we report, to our knowledge, the first trial directly comparing the effects of a GLP-1 RA (lixisenatide) in Japanese and Caucasian populations. The significant ($p = 0.0074$) treatment-by-ethnicity interaction seen in this trial in terms of improvement of PPG control indicates that Japanese patients experienced a greater benefit with lixisenatide than Caucasian patients. This finding may

be attributable to the lower levels of endogenous GLP-1 RAs in Japanese patients [11,12], and possibly also the fact that Japanese patients had, in general, a lower body weight and BMI at baseline. Differences in disease characteristics between patients of the two ethnicities investigated herein may indicate that a prandial treatment, such as lixisenatide, has a more profound effect in Japanese patients.

Significant improvements were also seen with lixisenatide QD and BID versus placebo in the overall population in terms of change from baseline in 2-h PPG after a standardized breakfast on the last day of treatment at the highest well-tolerated dose. Substantial body weight loss was reported for Caucasian patients treated with lixisenatide QD and BID; however, a large placebo effect on body weight reduction was observed in Japanese patients which complicated interpretation of this outcome for this ethnic group.

Lixisenatide safety was similar for both ethnicities in this trial. Gastrointestinal disorders (nausea, vomiting and diarrhoea) were the most frequent TEAEs and had a similar pattern in Japanese and Caucasian patients; nausea and vomiting occurred more frequently with active treatment compared with placebo. Events of symptomatic hypoglycaemia were observed in patients of both ethnicities in this trial, which was expected due to the co-administration of sulphonylureas, a known risk factor for the development of hypoglycaemia when combined with GLP-1 RAs [30].

The findings of this pharmacodynamics trial supported the use of lixisenatide 20 µg QD in phase III trials in Japanese patients [26]. In Japanese and Caucasian patients in this study, and in Caucasian patients in the dose-finding study [31], the lixisenatide 20 µg QD dose selected for maintenance had a favourable safety profile compared with a BID regimen, was well tolerated and provided the best acceptability in terms of patient convenience. Moreover, the efficacy and safety of lixisenatide in Japanese patients with T2DM has been investigated further in various treatment settings [32,33] and lixisenatide has been approved recently in Japan.

In conclusion, once-daily prandial GLP-1 RA lixisenatide significantly reduced PPG AUC_[0;29–4;30 h] versus placebo at the highest well-tolerated dose and had a good safety and tolerability profile in Japanese and Caucasian patients with T2DM treated with sulphonylureas with or without metformin. Japanese patients experienced particular benefits with lixisenatide in terms of reductions in PPG excursions.

Acknowledgements

PDY6797 was sponsored by Sanofi. Editorial assistance was provided to the authors by Jane Bryant PhD of Caudex Medical and was funded by Sanofi. The authors would like to thank the data monitoring committee members: Yuichiro Yamada MD, Akita University School of Medicine, Akita City, Japan; Takashi Sasaki MD, Kashiwa Hospital, The Jikei University School of Medicine, Kashiwa City, Japan; and Emmanuel Quinaux MSc, International Drug Development Institute, Louvain-la-Neuve, Belgium. The central laboratory for this trial (used in analysing efficacy and safety parameters) was BARC, Industriepark Zwijsnaarde 3B, B-9052 Ghent, Belgium.

The authors would also like to thank the PDY6797 trial investigators: Michael D'Emden and Andrew Lowy (Australia); Thomas Forst, Markolf Hanefeld, Frank Wagner (Germany); Kensuke Fuyuko, Hiroshi Hayakawa, Akira Imamura, Shigeto Kanada, Hideaki Jinnouchi, Hirose Kasahara, Ikkyou Kawa, Shuichi Maeda, Sunao Matsubayashi, Hiroshi Morita, Hirokata Nagashima, Keiko Nakano, Hajime Onde, Yamito Saito, Kazuo Satake, Shigeichi Shoji, Yasuo Toh, Masuo Tokoo, Yasuchi Wakida, Shintaro Yano, Hitoshi Yoshida (Japan); Francois Burger, Graham Ellis, Jacques Malan (South Africa); Annette Bak, Hendrik Reintke, Gerard Rongen (the Netherlands).

Conflict of Interest

G. B., E. N. and A. T. are employees of Sanofi. Y. S. has been a medical advisor to Astellas Pharma, Becton, Dickinson and Company, Boehringer Ingelheim, Eli Lilly and Company, GlaxoSmithKline, Johnson & Johnson, NovoNordisk A/S, Otsuka Pharmaceutical Group, Sanofi, Taisho Pharmaceutical Co., and Takeda Pharmaceutical Company, Ltd. D. R. has been a member of advisory boards and a speaker at symposia for Bristol-Myers Squibb, Eli Lilly, Medtronic, Merck Serono, MSD, Novartis, Novo Nordisk and Sanofi.

Y. S. executed the study, collected and interpreted the data, and wrote the manuscript. A. T. interpreted the data and wrote the manuscript. G. B. designed the study, collected and interpreted the data, and wrote the manuscript. E. N. designed the study, collected and interpreted the data, and wrote the manuscript. D. R. interpreted the data and wrote the manuscript.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Summary of patient disposition. mITT, modified intent-to-treat; PP, per protocol.

Table S1. Summary of treatment-emergent adverse events (TEAEs) by organ system experienced by ≥5% of patients in any treatment group in either ethnicity – safety population.

References

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* 2004; **66**(Suppl. 1): S37–S43.
2. Iwahashi H, Okauchi O, Ryo M et al. Insulin-secretion capacity in normal glucose tolerance, impaired glucose tolerance, and diabetes in obese and non-obese Japanese patients. *J Diabetes Investig* 2012; **3**: 271–275.
3. Jensen CC, Cnop M, Hull RL, Fujimoto WY, Kahn SE. Beta-cell function is a major contributor to oral glucose tolerance in high-risk relatives of four ethnic groups in the U.S. *Diabetes* 2002; **51**: 2170–2178.
4. Cho YS, Chen CH, Hu C et al. Meta-analysis of genome-wide association studies identifies eight new loci for type 2 diabetes in east Asians. *Nat Genet* 2012; **44**: 67–72.
5. Yasuda K, Miyake K, Horikawa Y et al. Variants in KCNQ1 are associated with susceptibility to type 2 diabetes mellitus. *Nat Genet* 2008; **40**: 1092–1097.

6. Neville SE, Boye KS, Montgomery WS, Iwamoto K, Okamura M, Hayes RP. Diabetes in Japan: a review of disease burden and approaches to treatment. *Diabetes Metab Res Rev* 2009; **25**: 705–716.
7. Seino Y, Fukushima M, Yabe D. GIP and GLP-1, the two incretin hormones: similarities and differences. *J Diabetes Investig* 2010; **1**: 8–23.
8. Seino Y, Yabe D. GIP and GLP-1: incretin actions beyond the pancreas. *J Diabetes Investig* 2013; **4**: 108–130.
9. Bagger JI, Knop FK, Lund A, Vestergaard H, Holst JJ, Vilsbøll T. Impaired regulation of the incretin effect in patients with type 2 diabetes. *J Clin Endocrinol Metab* 2011; **96**: 737–745.
10. Lee S, Yabe D, Seino Y, Hirano T. Intact glucagon-like peptide-1 levels are not decreased in Japanese patients with type 2 diabetes. *J Diabetes Investig* 2010; **1**: 73.
11. Yabe D, Kuroe A, Watanabe K et al. Little enhancement of meal-induced GLP-1 secretion in Japanese: comparison of type 2 diabetes and healthy controls. *J Diabetes Investig* 2010; **1**: 56–59.
12. Yabe D, Watanabe K, Sugawara K et al. Comparison of incretin immunoassays with or without plasma extraction: Incretin secretion in Japanese patients with type 2 diabetes. *J Diabetes Investig* 2012; **3**: 70–79.
13. Garber AJ, Abrahamson MJ, Barzilay JI et al. American association of clinical endocrinologists' comprehensive diabetes management algorithm 2013 consensus statement - executive summary. *Endocr Pract* 2013; **19**: 536–557.
14. Ryden L, Standl E, Bartnik M et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2007; **28**: 88–136.
15. Kohro T, Yamazaki T, Sato H et al. Trends in antidiabetic prescription patterns in Japan from 2005 to 2011. *Int Heart J* 2013; **54**: 93–97.
16. Werner U, Haschke G, Herling AW, Kramer W. Pharmacological profile of lixisenatide: a new GLP-1 receptor agonist for the treatment of type 2 diabetes. *Regul Pept* 2010; **164**: 58–64.
17. Gao Y, Yoon KH, Chuang LM et al. Efficacy and safety of exenatide in patients of Asian descent with type 2 diabetes inadequately controlled with metformin or metformin and a sulphonylurea. *Diabetes Res Clin Pract* 2009; **83**: 69–76.
18. Inagaki N, Ueki K, Yamamura A, Saito H, Imaoka T. Long-term safety and efficacy of exenatide twice daily in Japanese patients with suboptimally controlled type 2 diabetes. *J Diabetes Investig* 2011; **2**: 448–456.
19. Kadowaki T, Namba M, Yamamura A, Sowa H, Wolka AM, Brodows RG. Exenatide exhibits dose-dependent effects on glycemic control over 12 weeks in Japanese patients with suboptimally controlled type 2 diabetes. *Endocr J* 2009; **56**: 415–424.
20. Kadowaki T, Namba M, Imaoka T. Improved glycemic control and reduced bodyweight with exenatide: a double-blind, randomized, phase 3 study in Japanese patients with suboptimally controlled type 2 diabetes over 24 weeks. *J Diabetes Investig* 2011; **2**: 210–217.
21. 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* 2010; **12**: 341–347.
22. Kaku K, Rasmussen MF, Nishida T, Seino Y. Fifty-two-week, randomized, multicenter trial to compare the safety and efficacy of the novel glucagon-like peptide-1 analog liraglutide vs glibenclamide in patients with type 2 diabetes. *J Diabetes Investig* 2011; **2**: 441–447.
23. 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* 2008; **81**: 161–168.
24. 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* 2010; **26**: 1013–1022.
25. Seino Y, Rasmussen MF, Nishida T, Kaku K. Glucagon-like peptide-1 analog liraglutide in combination with sulphonylurea safely improves blood glucose measures vs sulphonylurea monotherapy in Japanese patients with type 2 diabetes: results of a 52-week, randomized, multicenter trial. *J Diabetes Investig* 2011; **2**: 280–286.
26. Seino Y, Min KW, Niemoeller E, Takami A. Randomized, double-blind, placebo-controlled trial of the once-daily GLP-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulphonylurea (GetGoal-L-Asia). *Diabetes Obes Metab* 2012; **14**: 910–917.
27. Yang W, Chen L, Ji Q et al. Liraglutide provides similar glycaemic control as glimepiride (both in combination with metformin) and reduces body weight and systolic blood pressure in Asian population with type 2 diabetes from China, South Korea and India: a 16-week, randomized, double-blind, active control trial(*). *Diabetes Obes Metab* 2011; **13**: 81–88.
28. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2005; **28**: S37.
29. Saloranta C, Guitard C, Pecher E et al. Nateglinide improves early insulin secretion and controls postprandial glucose excursions in a prediabetic population. *Diabetes Care* 2002; **25**: 2141–2146.
30. Bodmer M, Meier C, Krahenbuhl S, Jick SS, Meier CR. Metformin, sulphonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycemia: a nested case-control analysis. *Diabetes Care* 2008; **31**: 2086–2091.
31. Ratner RE, Rosenstock J, Boka G. Dose-dependent effects of the once-daily GLP-1 receptor agonist lixisenatide in patients with Type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled trial. *Diabet Med* 2010; **27**: 1024–1032.
32. Fonseca VA, Alvarado-Ruiz R, Raccach D et al. Efficacy and safety of the once-daily GLP-1 receptor agonist lixisenatide in monotherapy: a randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes (GetGoal-Mono). *Diabetes Care* 2012; **35**: 1225–1231.
33. Ratner RE, Hanefeld M, Shamanna P, Min K, Boka G, Miossec P, Muehlen-Bartmer I, Rosenstock J. Efficacy and safety of lixisenatide once-daily versus placebo in patients with T2DM insufficiently controlled on sulphonylurea +/- metformin (GetGoal-S). EASD Annual Meeting, 12–16 September 2011, Lisbon, Portugal.