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Equal improvement in glycaemia with lixisenatide given before breakfast or the main meal of the day

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ABSTRACT

Aims: The aim of this study is to explore whether administration timing affects glycaemic control by lixisenatide once-daily in type 2 diabetes mellitus (T2DM).
Methods: A phase IIIb, open-label, 1:1 randomized, active-controlled, 24-week multicentre study of T2DM patients inadequately controlled on metformin was conducted. Patients were administered lixisenatide before breakfast or the main meal. The primary endpoint was change from baseline at week 24 in glycated haemoglobin (HbA1c). Other endpoints: changes in body weight, fasting plasma glucose (FPG), 7-point self-monitored plasma glucose (SMPG) and Diabetes Treatment Satisfaction Questionnaire status (DTSQs) score. Adverse events (AEs) were monitored.
Results: Mean change in HbA1c from baseline at week 24 was −0.65% (−7.1 mmol/mol; main meal) and −0.74% (−8.1 mmol/mol; breakfast). Mean changes in FPG, body weight and DTSQs score were comparable between groups. The mean change in body weight (kg) was −2.60 (main meal) and −2.80 (breakfast group). The 7-point SMPG profiles showed greatest reductions in postprandial glucose after the meal at which lixisenatide was administered, with a residual effect seen on the subsequent meal. AE rates were similar between groups, including gastrointestinal AEs.
Conclusions: Lixisenatide before the main meal was noninferior to lixisenatide before breakfast in patients insufficiently controlled on metformin. Lixisenatide treatment allows flexibility in administration timing.

1. Introduction

Postprandial and fasting plasma glucose (PPG and FPG) contribute to glycated haemoglobin (HbA1c) levels, and addressing both is necessary to achieve sustained glycaemic control in patients with type 2 diabetes mellitus (T2DM) (American Diabetes Association, 2013; Garber et al., 2013).

Postbreakfast glucose excursions are a universal phenomenon that occur early in T2DM evolution (Monnier et al., 2002). Morning hyperglycaemia is thought to occur due to a deficit in insulin secretion in patients with T2DM, acting in concert with circadian variations in hepatic glucose output, which peaks in the early morning due to overnight fasting (Bavenholm, Pigon, Ostenson, & Efendic, 2001; Boden, Chen, & Urbain, 1996). As such, effective management of postbreakfast hyperglycaemia is an important treatment target in patients with T2DM (Monnier et al., 2002). Many patients experience substantial PPG excursions after meals other than breakfast, and blood glucose changes have been shown to be driven by carbohydrate intake in patients who respond to treatment (Franc et al., 2010). For example, when moderate- and high-carbohydrate lunches were compared in metformin-treated patients with T2DM, the high-carbohydrate lunch significantly increased postprandial peak glucose levels and prolonged the time taken for glucose to return to preprandial levels (Powers, Cuddihy, Wesley, & Morgan, 2010). It is

Conflicts of Interest: B.A. has received honoraria for lecturing and/or consultancy for AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, GSK, Merck, Novartis, Novo Nordisk, Sanofi and Takeda, which all produce DPP-4 inhibitors or GLP-1 receptor agonists. N.V. has nothing to disclose. R.A. has received speaker and consulting fees from Sanofi, Novo Nordisk, Bristol-Myers Squibb, AstraZeneca, Eli Lilly, Boehringer Ingelheim, Janssen, Takeda, Medtronic and Becton Dickinson.

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therefore also important to control PPG excursions after meals other than breakfast, which could be achieved with prandial medications with flexible administration timing.

Lixisenatide is a once-daily prandial glucagon-like peptide-1 receptor agonist (GLP-1 RA) for the treatment of T2DM. Lixisenatide mimics the effects of endogenous GLP-1, increasing insulin secretion and suppressing glucagon release (Christensen, Knop, Vilsboll, & Holst, 2011). Lixisenatide also delays gastric emptying, which prolongs glucose absorption, improving control of PPG excursions (Lorenz et al., 2013). Lixisenatide is a modified form of exendin-4 (a partial GLP-1 homolog), with a C-terminus of six lysine residues, allowing it to withstand degradation by dipeptidyl peptidase 4, and prolonging activity.

With the exception of the GetGoal-M study (Ahrén, Leguizamo, Miossec, Saubadu, & Aronson, 2013), which assessed morning and evening lixisenatide dosing, studies in the phase III GetGoal program investigated the efficacy and safety of lixisenatide administered before breakfast. Timings of administration and dose were kept consistent across the majority of GetGoal studies to reduce potential confounding factors, which established the efficacy of a set lixisenatide regimen administered as a monotherapy or in combination with other agents in patients poorly controlled on oral antidiabetic drugs (OADs) or basal insulin (Ahrén et al., 2013; Bolli et al., 2013; Fonseca et al., 2012; Pinget et al., 2013; Riddle, Aronson, et al., 2013; Riddle, Forst, et al., 2013; Rosenstock et al., 2013; Seino, Min, Niemoeller, & Takami, 2012). This study is the first to assess the efficacy of lixisenatide dosing prior to the main meal.

2. Materials and methods

2.1. Study design

This was a 24-week, phase IIIb, open-label, 1:1 randomized, active-controlled, two-arm, parallel-group, multicentre study of patients with T2DM inadequately controlled on metformin (Supplementary Fig. 1). This study aimed to demonstrate the noninferiority of lixisenatide 20 μg once-daily administered within the hour before the main meal of the day (breakfast, lunch or dinner) compared with within the hour before breakfast in terms of HbA1c change at week 24. The main meal of the day was defined at visit 2 based on each patient's answer to the question: “On most days, at which meal do you eat the largest amount of food?” The main meal of the day was also independently determined by a dietician. Patients were stratified by randomization strata of the main meal of the day, as determined by the patients, and by screening of HbA1c (<8% [<64 mmol/mol] or ≥8% [≥64 mmol/mol]). The study was conducted across 10 countries (Canada, the Czech Republic, France, Germany, Poland, Romania, the Russian Federation, Spain, Ukraine, the USA) between February 2012 and May 2013 (see Appendix 1 for participating investigators).

Lixisenatide 10 μg once-daily was administered for the first 2 weeks of the study and then continued at 20 μg once-daily until study end. A reduction to 10 μg per day could be made if 20 μg per day was not tolerated, but an attempted increase to 20 μg per day had to be made within 4 weeks; if the attempted increase failed, the patient was maintained on 10 μg per day throughout the study. All regimens were administered subcutaneously using the Opticlik® (Sanofi, Paris, France) self-injector device.

In the main meal group and breakfast group, lixisenatide was administered within the hour before the main meal and the hour before breakfast, respectively.

2.2. Inclusion criteria

All patients in this study met the following criteria at screening: T2DM for ≥1 year; treated with metformin at a stable dose of ≥1.5 g/day for ≥3 months; and HbA1c ≥7% (53 mmol/mol) and ≤10% (86 mmol/mol).

2.3. Study populations

The safety population was the randomized and treated population, defined as all randomized patients who were exposed to at least one dose of the lixisenatide, regardless of length of treatment. Efficacy analyses were based on the modified intent-to-treat (mITT) population corresponding with all randomized patients who received at least one dose of lixisenatide and had a baseline assessment and at least one postbaseline assessment of any primary or secondary efficacy endpoint.

2.4. Endpoints

The primary endpoint of this phase IIIb study was change in HbA1c from baseline to week 24 with lixisenatide administered within the hour before breakfast or the main meal of the day. Secondary endpoints included: the proportion of HbA1c responders (HbA1c <7% [<53 mmol/mol] or ≤6.5% [≤48 mmol/mol] at week 24); change in body weight, FPG and 7-point self-monitored plasma glucose (SMPG) from baseline at week 24. Change in treatment satisfaction from baseline to week 24 was also assessed by the Diabetes Treatment Satisfaction Questionnaire status (DTSQs) score in participating countries and where validated. Total score was calculated as sums of items 1 and 4–8 (Supplementary Table 1), which measured treatment satisfaction. Each item was scored on a 7-point scale, ranging from 0 (very dissatisfied) to 6 (very satisfied). Items 2 and 3 were treated individually (Bradley, 1994). Safety endpoints were adverse events (AEs), serious AEs, symptomatic hypoglycaemia, vital signs and safety laboratory values, which were monitored throughout the study. Symptomatic hypoglycaemia was defined as an event with clinical symptoms that were considered to be a result of a hypoglycaemic episode with plasma glucose <60 mg/dl (3.3 mmol/l) or, if no plasma glucose measurement was available, was associated with prompt recovery after oral carbohydrates, intravenous glucose or glucagon administration. Severe hypoglycaemia was defined as clinical symptoms that the patient could not manage alone due to acute neurological impairment and required assistance from another person, and plasma glucose <36 mg/dl (2.0 mmol/l) or, if a plasma glucose level was not available, the event was associated with a prompt recovery after carbohydrates, intravenous glucose or glucagon administration. Treatment-emergent AEs (TEAEs) were defined as AEs that developed or worsened during open-label treatment and for up to 3 days after the last administration of lixisenatide.

This study also examined the following composite endpoints at week 24: HbA1c levels <7% and no confirmed (plasma glucose <60 mg/dl [3.3 mmol/l]) symptomatic hypoglycaemia; HbA1c levels <7% and no weight gain; HbA1c levels <7%, no symptomatic hypoglycaemia and no weight gain; HbA1c levels <7% and 2-hour PPG <140 mg/dl after the main meal or breakfast.

2.5. Statistical methods

The statistical test for change in HbA1c from baseline at week 24 was one-sided, with alpha levels of 0.025 using a noninferiority margin of 0.4% HbA1c. The primary endpoint was analyzed using an analysis of covariance (ANCOVA) model, with treatment (lixisenatide administered within the hour before the main meal of the day or within the hour before breakfast), randomization strata of main meal of the day (breakfast, lunch or dinner), randomization strata of screening HbA1c (<8% [<64 mmol/mol] or ≥8% [≥64 mmol/mol]) and country as fixed effects, and using the baseline HbA1c value as a covariate. Baseline values were defined as the last available value taken before the first dose of lixisenatide was administered. The difference between treatment groups and two-sided 95% confidence intervals (CIs) was estimated within the framework of the ANCOVA model. Noninferiority was demonstrated if the upper boundary of the two-sided 95% CIs was ≤0.4%.

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Table 1
Demographics and clinical characteristics at screening or at baseline—randomized population.

Parameter	Main meal ($n = 225$)	Breakfast ($n = 226$)
Age, mean years (SD)	56.3 (10.6)	57.5 (9.7)
Male/female, %	44.9/55.1	42.9/57.1
Race, *n* (%)		
Caucasian	211 (93.8)	211 (93.4)
Black	4 (1.8)	8 (3.5)
Asian	10 (4.4)	7 (3.1)
Other	0	0
Duration of diabetes, mean years (SD)	6.7 (4.9)	7.8 (5.6)
BMI, mean kg/m^2 (SD)	33.5 (4.5)	32.8 (4.6)
Patients in each BMI category (%)		
<30 kg/m^2	22.7	26.5
≥30 kg/m^2	77.3	73.5
Body weight, mean kg (SD)	95.0 (16.1)	92.9 (17.2)
FPG, mean mmol/l (SD)*	9.2 (2.0)	9.3 (2.0)
HbA1c, mean % (SD)	7.85 (0.76)	7.93 (0.78)
Daily metformin dose, mean mg (SD)	2040.7 (390.0)	2091.2 (1255.3)
Duration of metformin treatment, mean years (SD)	4.8 (4.1)	5.6 (4.6)

FPG, $n = 225$ for both treatment groups.
BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; mITT, modified intent-to-treat; SD, standard deviation.

Table 2
Efficacy outcomes at week 24—mITT population.

Outcomes	Main meal ($n = 224$)	Breakfast ($n = 226$)	LS mean difference (s.e.) for main meal versus breakfast [95% CI]
n	218	222	
LS mean change in HbA1c, % (mmol/mol); [s.e.]	−0.65 (−7.1) [0.074]	−0.74 (−8.1) [0.074]	0.09 (1.0) [0.079] [−0.067, 0.242]
Responders in each category, *n* (%)			
≤6.5% (48 mmol/mol)	49 (22.5)	57 (25.7)	−3.1 [−11.03,4.75]
<7.0% (53 mmol/mol)	95 (43.6)	95 (42.8)	1.0 [−7.91, 9.91]
n	202	200	
LS mean change in average 7-point SMPG, mmol/l (s.e.)	−0.80 (0.145)	−1.10 (0.145)	0.30 (0.154) [−0.008 to 0.598]
n	220	224	
LS mean change in body weight, kg (s.e.)	−2.60 (0.320)	−2.80 (0.319)	0.21 (0.339) [−0.46, 0.87]
n	220	222	
LS mean change in FPG, nmol/l (s.e.)	−0.35 (0.192)	−0.57 (0.193)	0.22 (0.200) [−0.176, 0.611]
n	224	226	
LS mean change in DTSQs score (s.e.)	3.01 (0.546)	3.54 (0.529)	−0.53 (0.549) [−1.609, 0.550]

CI, confidence interval; DTSQs, Diabetes Treatment Satisfaction Questionnaire status; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; LS, least squares; mITT, modified intent-to-treat; s.e., standard error; SMPG, self-monitored plasma glucose.

All continuous secondary endpoints were analyzed using the ANCOVA model. All categorical efficacy parameters were analyzed using the Cochran–Mantel–Haenszel method stratified by the randomization strata of main meal of the day and HbA1c at screening. The difference between groups in terms of the number of patients with symptomatic hypoglycaemia was analyzed based on the two-sided Fisher's exact test. Safety analyses were descriptive and were performed using the safety population.

3. Results

A total of 451 patients were randomized: 225 patients were randomized to the main meal group and 226 patients were randomized to the breakfast group. One hundred and eighty-nine (84.0%) and 202 (89.4%) patients from the main meal and breakfast groups, respectively, completed the study, with the most common reason for discontinuation in both groups cited as the occurrence of AEs (4.4 and 4.9% of patients in the main meal and breakfast groups, respectively). All patients were included in the safety population. One patient was exposed to lixisenatide for 1 day but did not have any postbaseline efficacy measures and was not included in the mITT population; otherwise, the mITT population and safety populations were identical (Supplementary Fig. 2).

Patient demographics and baseline characteristics were comparable across groups, with the exception of patients in the breakfast group having a slightly longer duration of diabetes and metformin treatment at baseline compared with the main meal group (Table 1).

A similar proportion of patients and dieticians considered the same meal of the day to be the 'main' meal, with the patient determining the main meal by answering the question: "On most days, at which meal do you eat the largest amount of food?", while the dietician assessed calorie intake and meal composition. In total, 8.2, 53.0 and 38.8% classified breakfast, lunch or dinner as the main meal, compared with 10.2, 53.5 and 36.3% classified by dieticians, respectively. In the mITT population, patients and dieticians defined the same meal as the main meal in 86.2 and 81.9% of cases in the main meal and breakfast groups, respectively.

3.1. Change in HbA1c

Lixisenatide administration within the hour before the main meal (breakfast, lunch or dinner) was noninferior in terms of change in HbA1c to lixisenatide administration within the hour before breakfast in patients with T2DM inadequately controlled on metformin. The least squares (LS) mean change (standard error [s.e.]) in HbA1c from baseline at week 24 was −0.65% (0.074%) or −7.1 mmol/mol (0.8 mmol/mol) for the main meal group and −0.74% (0.074%) or −8.1 mmol/mol (0.8 mmol/mol) for the breakfast group (LS mean difference for the main meal versus breakfast groups: 0.09% [1.0 mmol/mol; 95% CI: −0.07%, 0.24%]; $p = 0.2664$) (Table 2; Fig. 1A). Based on the prespecified primary analysis, noninferiority of the main meal group compared with the breakfast group was demonstrated, as the upper bound of the two-sided 95% CI of the LS mean difference was less than the predefined noninferiority margin of 0.4%.

3.2. Proportion of HbA1c responders

Comparable proportions of patients in the two groups were HbA1c responders. The proportions of patients in the main meal group who achieved HbA1c ≤6.5% (48 mmol/mol) or <7% (53 mmol/mol) were 22.5 and 43.6%, respectively, compared with 25.7 and 42.8%, respectively, in the breakfast group (Table 2).

3.3. FPG and body weight

Comparable reductions in FPG (Table 2) and body weight (Table 2; Fig. 1B) were seen in the two groups. The LS mean (s.e.) change in FPG was −0.35 (0.192) and −0.57 (0.193) mmol/l for the main meal and breakfast groups, respectively. The LS mean (s.e.) change in body weight (kg) from baseline to week 24 was −2.60 (0.320) for the main meal group and −2.80 (0.319) for the breakfast group.

3.4. SMPG profiles

From the SMPG profiles, the average 7-point SMPG was estimated for the main meal group and the breakfast group. The LS mean change (s.e.) from baseline in average 7-point SMPG at week 24 was −0.80 (0.145) mmol/l for the main meal group and −1.10 (0.145) mmol/l for the breakfast group (Table 2). Fig. 1C shows the SMPG profiles at baseline and week 24 for the breakfast group (as randomized) and

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main meal group (separated according to breakfast, lunch or dinner). All main meal subgroups, and the breakfast group, showed lower pre-breakfast glucose values (fasting values) at week 24 than at baseline. Within the main meal group, differences were observed depending on the time of lixisenatide administration. In the main meal subgroups, a large reduction in glucose was observed after the meal at which lixisenatide was administered, with a less pronounced effect observed at the subsequent meal in the breakfast and lunch subgroups. It was also found that bedtime glucose was reduced to a larger degree in the main meal group when lixisenatide was given before dinner compared with before breakfast or lunch (mean change from baseline at week 24 glucose at bedtime was −0.03, −0.93 and −1.04 mmol/l for the breakfast, lunch and dinner groups, respectively). The mean change at bedtime from baseline at week 24 in patients randomized to breakfast was −1.04 mmol/l.

3.5. Composite endpoints

The percentage of patients reaching HbA1c <7% with no symptomatic hypoglycaemia at week 24 was 40.4% for the main meal group and 41.0% for the breakfast group (response rate [r.r.] difference = −0.5% [95% CI −9.39 to 8.44%]). A comparable proportion of patients in both treatment groups reached HbA1c <7% with no weight gain at week 24 (40.8 and 38.6% in the main meal and breakfast group, respectively; r.r. difference = 2.4% [95% CI −6.39 to 11.24%]) and HbA1c <7% with no weight gain at week 24 and no hypoglycaemia during the treatment period (38.1 and 37.2% in the main meal and breakfast group, respectively; r.r. difference = 1.0% [95% CI −7.82 to 9.77%]). The percentage of patients achieving HbA1c <7% and 2-hour PPG <140 mg/dl at week 24 was 28.9% for the main meal group and 27.6% for the breakfast group (r.r. difference = 1.5% [95% CI −6.62 to 9.64%]).

3.6. DTSQs score

The LS mean (s.e.) change in DTSQs was 3.01 (0.546) and 3.54 (0.529) for the main meal and breakfast group, respectively; LS mean difference of −0.53 (95% CI −1.609 to 0.550).

3.7. Adverse events

The mean duration of study treatment was 157.6 and 161.1 days in the main meal and breakfast groups, respectively. At the end of treatment, 95.6 and 96.5% of patients in the main meal and breakfast groups were receiving lixisenatide 20 μg once-daily, indicating that the maintenance dose was well-tolerated in most patients, irrespective of treatment group.

There were slightly fewer TEAEs in the main meal group than in the breakfast group. Percentages of patients reporting serious TEAEs and TEAEs leading to treatment discontinuation were similarly low (Supplementary Table 2).

A total of 55/225 (24.4%) and 58/226 (25.7%) patients in the main meal and breakfast groups, respectively, experienced gastrointestinal (GI) TEAEs. Consistent with the mechanism of action of lixisenatide as a GLP-1 RA, nausea was the most frequently reported AE in both groups, with an incidence of approximately 15% (Table 2; Supplementary data). Four (1.8%) patients from the main meal group and three (1.3%) from the breakfast group discontinued treatment due to nausea and/or vomiting.

Two patients reported allergic reactions that were positively adjudicated as allergic reactions by an independent allergic reaction assessment committee (ARAC): urticaria (1 [0.4%] patient in the main meal group) and asthma (1 [0.4%] patient in the breakfast group). Neither was adjudicated as possibly related to lixisenatide treatment by the ARAC.

Four (1.8%) patients in the main meal group and three (1.3%) in the breakfast group had a TEAE of increased lipase reported on the specific AE form for increase lipase and/or amylase >2 times the upper limit of normal. No cases of pancreatitis were reported during the study.

No patients in the main meal group and two patients in the breakfast group had a TEAE of increased calcitonin ≥20 pg/ml reported on the specific AE form for increased calcitonin: both patients had calcitonin levels >20 pg/ml on day 1 of the study, and the highest calcitonin value for these patients during the study was 27 and 43 pg/ml.

The incidence of symptomatic hypoglycaemia (according to protocol definition) was low in both groups: 5.8% (13/225) in the main meal group and 2.2% (5/226) in the breakfast group ($p = 0.0581$). The annualized rate of symptomatic hypoglycaemia per patient was 0.24 for the main meal group and 0.059 for the breakfast group. No patient from either group experienced severe symptomatic hypoglycaemia.

The timing of symptomatic hypoglycaemic events varied between the breakfast group and the main meal subgroups (Table 3). Six events were observed in patients randomized to the breakfast group. In the

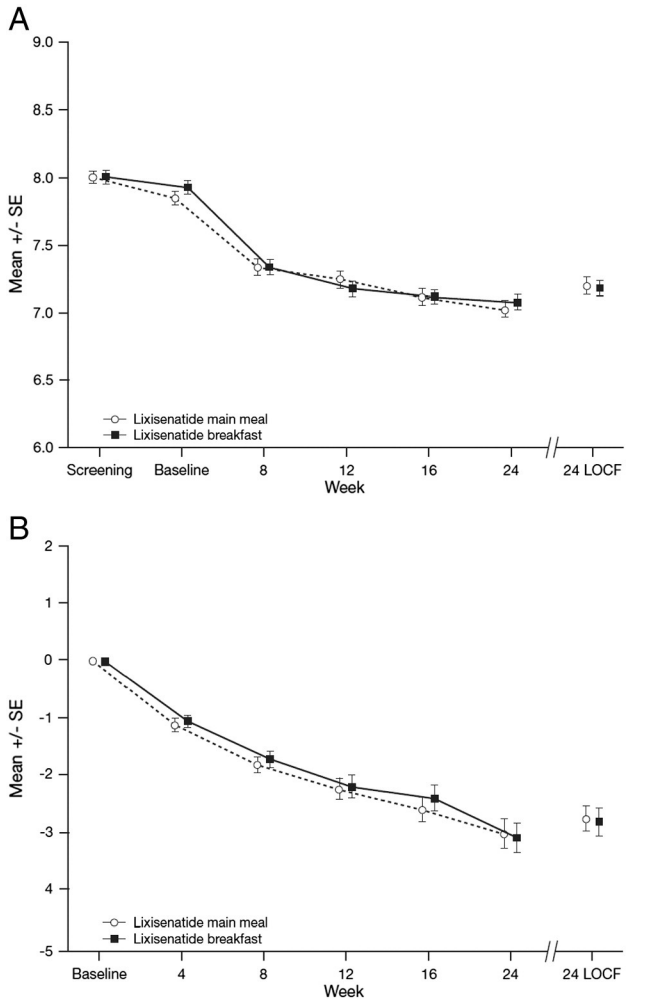

Fig. 1. A—mean HbA1c (%) by visit—mITT population. The plot included measurements obtained up to 14 days after the last injection of the investigational medicinal product. LOCF, last observation carried forward; SE, standard error. B—mean change in body weight (kg) from baseline by visit—mITT population. The plot included measurements obtained up to 3 days after the last injection of the investigational medicinal product. LOCF, last observation carried forward; SE, standard error. C—7-Point SMPG profiles (mmol/l) at each time point at baseline and Week 24—mITT population. The plot included measurements obtained up to the date of the last injection of the investigational medicinal product. *Includes patients from the main meal group with breakfast, lunch or dinner as the main meal of the day as defined by the patient at visit 2. LOCF, last observation carried forward; SE, standard error.

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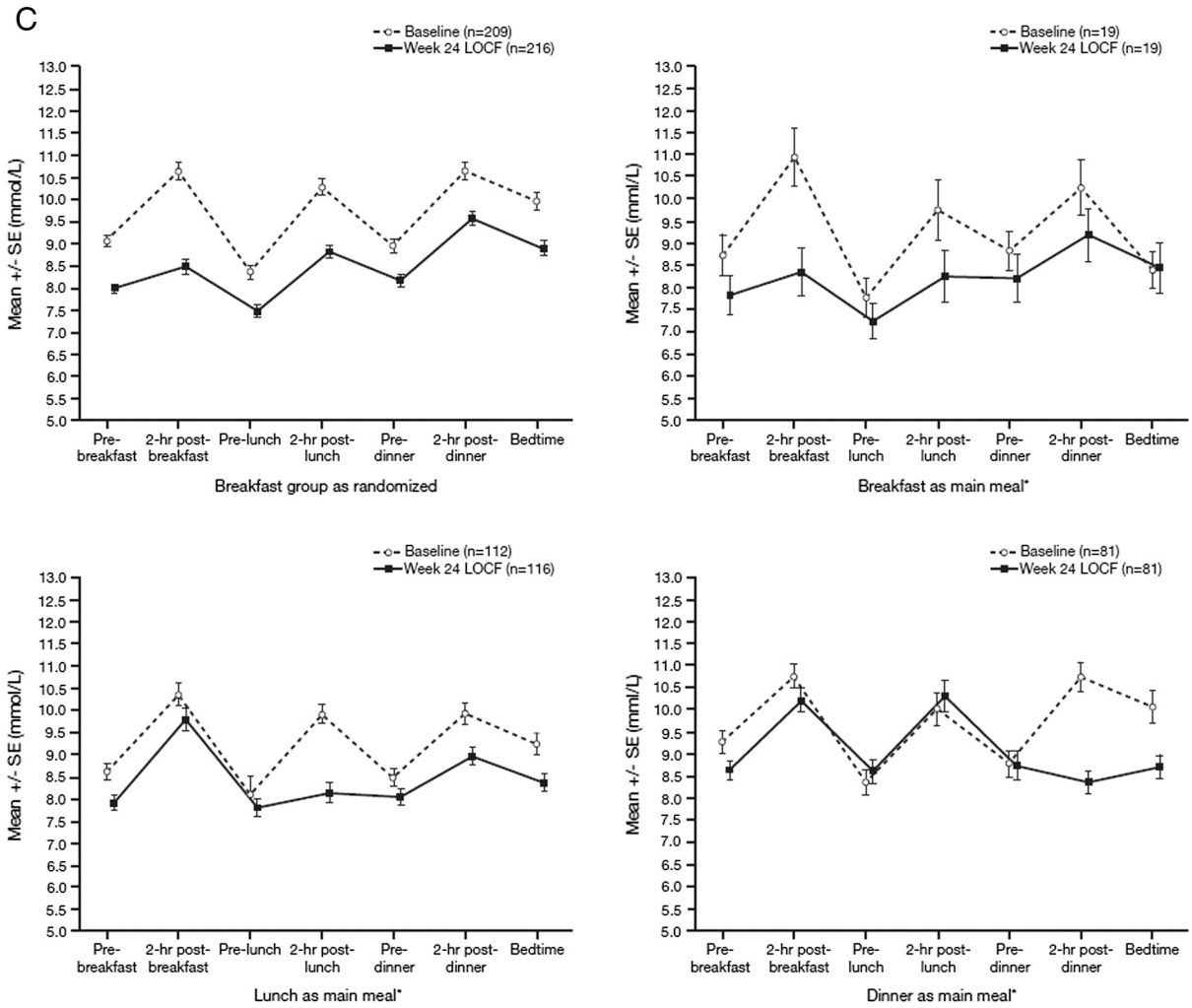

Fig. 1 (*continued*).

main meal group (n = 225), no events were observed in the breakfast subgroup, 12 were observed in the lunch subgroup and 12 in the dinner subgroup.

4. Discussion

This phase IIIb study indicated that reductions in HbA1c by lixisenatide were similar, regardless of whether it was administered before breakfast or before the main meal of the day. These findings offer patients flexibility in the timing of administration, allowing users to manage their PPG excursions according to their eating habits and personal needs. Similar rates (approximately 40%) of patients in the main meal and breakfast groups reached the HbA1c target of 7% (53 mmol/mol). Body weight loss, change in average SMPG profiles, FPG reductions, change in DTSQs score and composite endpoints were also comparable between the groups. Lixisenatide was well-tolerated, and the occurrence of symptomatic hypoglycaemia and GI TEAEs was as expected for GLP-1 RAs in combination with stable metformin.

The current study used a simple approach to define the main meal of the day, with the patient making the determination at the second study visit. Interestingly, that determination was found to be consistent with an objective dietician review of each patient's typical meal intake pattern, indicating that assistance from a dietician would not have significantly affected outcomes. Assessing the differences and similarities between patients and dieticians in the determination of the main meal is a unique characteristic of this study.

This study was performed across multiple countries. Overall results demonstrate that dieticians and patients define the main meal of the day in the same way, regardless of possible differences in how different nationalities define their main meal. In the future, further analysis could be performed taking into consideration cultural differences.

Flexibility in the timing of medications with predominantly prandial activity may be desirable to optimize patient adherence by allowing the freedom to administer therapy with either breakfast or the main meal. This flexibility may be of benefit to healthcare providers. It was recently demonstrated that treatment with GLP-1 RAs is associated with good patient satisfaction rates (Davies & Speight, 2012). Indeed, flexibility in dose

Table 3
Symptomatic hypoglycaemia during the on-treatment period by hour of the day.

Time of day	Main meal ($n = 225$)[a]			Breakfast ($n = 226$)[b]
	Breakfast ($n = 19$)	Lunch ($n = 119$)	Dinner ($n = 87$)	
Total number of events	0	12	12	6
23:00 to <06:00	0	1	0	1
06:00 to <10:00	0	1	0	0
10:00 to <14:00	0	2	0	1
14:00 to <18:00	0	5	0	2
18:00 to <23:00	0	3	12	2
Missing	0	0	0	0

[a] Patients from the main meal group with breakfast, lunch or dinner as main meal of the day as defined by the patient at visit 2.
[b] Patients who were randomized to the breakfast group.

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timing could result in greater improvements in compliance and acceptability. For example, inflexibility in the timing of insulin injections has been cited as a reason for nonadherence (Peyrot, Barnett, Meneghini, & Schumm-Draeger, 2012). Furthermore, a recent systematic review of 17 studies found that flexible regimens improved insulin therapy adherence (Davies et al., 2013). DTSQs data from this study found that lixisenatide improved treatment satisfaction independent of timing of administration in patients with T2DM insufficiently controlled on metformin, with improvement appearing to be driven partly by lowering of HbA1c and weight.

The 7-point SMPG profiles for patients treated before breakfast or the main meal of the day demonstrated that lixisenatide had the strongest effect in reducing PPG excursions after the meal at which it was administered. However, when lixisenatide was given before breakfast, PPG was also reduced after lunch and dinner, and when lixisenatide was given before lunch, PPG was also reduced after dinner, although the effects on PPG excursions at the subsequent meal were less pronounced. Taken together, these data indicate that lixisenatide had a longer pharmacodynamic effect than expected from its short half-life, and covers meals other than those at which it is administered. This conclusion is supported by a recent study from Lorenz and colleagues, which evaluated the effects of lixisenatide on PPG (area under the curve and peak levels) after a standardized meal at breakfast, lunch and dinner, on gastric emptying at breakfast, and the relationship between the effects on PPG and gastric emptying. The results indicated that lixisenatide 20 μg administered once daily in the morning reduces PPG levels throughout the day, and that the reduction in PPG, at least after breakfast, is attributable to a delay in gastric emptying (Lorenz et al., 2013). The effect at bedtime was largest when lixisenatide was administered at dinner; this effect probably explains why there was no difference in reduction in HbA1c, regardless of when lixisenatide was given, even though the dinner dose covered only one meal, whereas breakfast and lunch dosing covered more than one meal.

Alternative timing of lixisenatide administration (dinner and breakfast administration) was also investigated in the GetGoal-M study. GetGoal-M was not designed to compare the efficacy of lixisenatide administered in the morning versus in the evening; instead, each regimen was compared with placebo. As such, although the improved glycaemia versus placebo was similar in the two groups, direct comparisons between morning and evening lixisenatide dosing could not be drawn (Ahrén et al., 2013). However, the effects observed in GetGoal-M were similar to those in this study, with an HbA1c decrease of −0.9% (9.8 mmol/mol) in the morning group and −0.8% (8.7 mmol/mol) in the evening group, and 43 and 40.6% of the patients reaching HbA1c target <7% (53 mmol/mol) in the morning and evening groups, respectively (Ahrén et al., 2013).

One limitation of this study was that there were no study centres in Asia. In the future it would be useful to look at the effect of lixisenatide administered before the main meal versus breakfast in Asian patients to assess whether dietary differences and the preponderance of sulphonylurea use affect the control of PPG excursions at different times of the day. Future studies could also assess the mechanism of the flexibility of administration timing and investigate whether this flexibility translates into increased patient compliance.

In patients with T2DM insufficiently controlled on metformin, prandial lixisenatide once-daily administered before breakfast or the main meal was equally well-tolerated and resulted in comparable reductions in HbA1c. This finding allows patients to select the most convenient administration timing without compromising glycaemic efficacy, beneficial effects on weight loss or tolerability of lixisenatide in order to facilitate the achievement of glycaemic targets.

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B.A. takes full responsibility for the work as a whole, including the study design, access to data and the decision to submit and publish the manuscript.

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Appendix 2. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jdiacomp.2014.05.012.

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