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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%.