Contrasting Effects of Lixisenatide and Liraglutide on Postprandial Glycemic Control, Gastric Emptying, and Safety Parameters in Patients With Type 2 Diabetes on Optimized Insulin Glargine With or Without Metformin: A Randomized, Open-Label Trial

Juris J. Meier,[1] Julio Rosenstock,[2] Agnès Hincelin-Méry,[3] Christine Roy-Duval,[3] Astrid Delfolie,[3] Hans-Veit Coester,[4] Bjoern A. Menge,[1] Thomas Forst,[5] and Christoph Kapitza[4]

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OBJECTIVE

This mechanistic trial compared the pharmacodynamics and safety of lixisenatide and liraglutide in combination with optimized insulin glargine with/without metformin in type 2 diabetes (T2D).

RESEARCH DESIGN AND METHODS

This was a multicenter, randomized, open-label, three-arm trial comparing lixisenatide 20 μg and liraglutide 1.2 and 1.8 mg once daily for 8 weeks in combination with insulin glargine after optimized titration. The primary end point was change from baseline to week 8 in incremental area under the postprandial plasma glucose curve for 4 h after a standardized solid breakfast (AUC $PPG_{0030–0430\ h}$). Changes from baseline in gastric emptying, 24-h plasma glucose profile, HbA_{1c}, fasting plasma glucose (FPG), 24-h ambulatory heart rate and blood pressure, amylase and lipase levels, and adverse events (AEs) were also assessed.

RESULTS

In total, 142 patients were randomized and treated. Lixisenatide 20 μg achieved greater reductions of AUC $PPG_{0030-0430\ h}$ compared with liraglutide (marginal mean [95% one-sided CI] treatment difference, −6.0 [−7.8] h · mmol/L [−108.3 (−140.0) h · mg/dL] vs. liraglutide 1.2 mg and −4.6 [−6.3] h · mmol/L [−83.0 (−114.2) h · mg/dL] vs. liraglutide 1.8 mg; $P < 0.001$ for both), and gastric emptying was delayed to a greater extent than with liraglutide 1.2 and 1.8 mg ($P < 0.001$ for treatment comparisons). FPG was unchanged in all treatment arms. At week 8, mean ± SD HbA_{1c} was 6.2 ± 0.4% (44 ± 5 mmol/mol), 6.1 ± 0.3% (44 ± 4 mmol/mol), and 6.1 ± 0.3% (44 ± 4 mmol/mol) for lixisenatide 20 μg and liraglutide 1.2 and 1.8 mg, respectively. At week 8, both liraglutide doses increased marginal mean ± SE 24-h heart rate from baseline by 9 ± 1 bpm vs. 3 ± 1 bpm with lixisenatide ($P < 0.001$). Occurrence of symptomatic hypoglycemia was higher with lixisenatide; gastrointestinal AEs were more common with liraglutide. Lipase levels were significantly increased from baseline with liraglutide 1.2 and 1.8 mg (marginal mean ± SE increase 21 ± 7 IU/L for both; $P < 0.05$).

CONCLUSIONS

Lixisenatide and liraglutide improved glycemic control in optimized insulin glargine-treated T2D albeit with contrasting mechanisms of action and differing safety profiles.

[1]Diabetes Division, St. Josef Hospital, Ruhr-University Bochum, Bochum, Germany
[2]Dallas Diabetes and Endocrine Center at Medical City, Dallas, TX
[3]Sanofi R&D, Chilly-Mazarin, France
[4]Profil, Neuss, Germany
[5]Profil, Mainz, Germany

Corresponding author: Juris J. Meier, juris.meier@rub.de.

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A slide set summarizing this article is available online.

Basal insulin replacement has become a well-established treatment approach when lifestyle measures and oral antidiabetic agents (OADs) are insufficient to reach individualized glycemic goals (1,2). Proper and systematic titration of basal insulin allows 50–60% of patients with T2D to reach glycemic goals (3–5). Basal insulin improves glycemic control predominantly by reducing nocturnal and fasting plasma glucose (FPG). However, many patients experience substantial postprandial glucose (PPG) excursions and are unable to achieve glycemic targets; even in those who do, or get close to target HbA_{1c}, additional improvements in diabetes control could be achieved if elevated PPG levels were further reduced (6–8).

It has been suggested that, after intensification of treatment with basal insulin, PPG contributes ~60% of hyperglycemia in patients with a mean HbA_{1c} of 7.0% (9). There is therefore a strong rationale for the use of basal insulin in combination with treatments that can reduce PPG in order to achieve further reductions in HbA_{1c}.

Lixisenatide (Lyxumia; Sanofi, Paris, France) is a once-daily prandial GLP-1 receptor agonist (GLP-1 RA) that acts primarily on PPG excursions through delaying gastric emptying and suppressing glucagon. The efficacy and tolerability of lixisenatide monotherapy or in combination with basal insulin and/or OADs for the improvement of glycemic control in patients with T2D were established in the GetGoal clinical trial program (10–14). The longer-acting GLP-1 RA liraglutide (Victoza; Novo Nordisk, Bagsvaerd, Denmark) has also demonstrated efficacy in terms of glycemic control and body weight reductions in patients with T2D in a large phase III clinical trial program (Liraglutide Effect and Action in Diabetes) (15–20). In these studies, liraglutide significantly reduced 24-h hyperglycemia, a finding that has been ascribed to its long half-life. Differences in the pharmacodynamics of these GLP-1 RAs have been shown in a 4-week, head-to-head trial of lixisenatide 20 μg and liraglutide 1.8 mg as add-on to metformin (clinical trial reg. no. NCT01175473) in patients with T2D inadequately controlled on metformin monotherapy. In this trial, lixisenatide demonstrated significantly greater reductions than liraglutide in the area under the plasma glucose curve (AUC $PPG_{0030–0430\ h}$) during a standardized breakfast meal test, whereas reductions in FPG were more pronounced with liraglutide (21).

The primary objective of this trial was to compare change in AUC $PPG_{0030–0430\ h}$ after a standardized solid breakfast in patients with T2D receiving 8 weeks of once-daily lixisenatide 20 μg, liraglutide 1.2 mg, or liraglutide 1.8 mg in combination with insulin glargine with/without metformin after a period of optimized insulin glargine titration in a treat-to-target design. As differences between GLP-1 RAs in terms of effects on gastric emptying and heart rate have previously been reported (21–23), these parameters were further and more precisely assessed in this trial.

RESEARCH DESIGN AND METHODS

Trial Design

This was a multicenter, randomized, open-label, active comparator-controlled, three parallel-arm trial conducted at eight centers in Germany. Patients were centrally randomized 1:1:1 (by interactive voice response system and stratified by HbA_{1c} [<8% or ≥8% and 64 mmol/mol or ≥64 mmol/mol], the use of metformin [yes/no], and study site) to receive lixisenatide 20 μg s.c. once daily, liraglutide 1.2 mg s.c. once daily, or liraglutide 1.8 mg s.c. once daily as add-on therapy to optimized insulin glargine for 8 weeks. The trial comprised the following (Supplementary Fig. 1): *1*) a period of up to 14 weeks that included a 2-week screening phase, a run-in period of a minimum of 4 weeks up to 11 weeks of insulin glargine optimal titration, and 1 week of baseline pharmacodynamic assessments; *2*) an open-label, randomized, 8-week treatment period (1–2 weeks at the initial liraglutide/lixisenatide dose and 6–7 weeks of treatment at the maintenance dose), with pharmacodynamic assessment at the end of treatment; and *3*) a follow-up period with an end-of-study visit 7 ± 2 days after the end of treatment.

All patients signed an informed consent form. The trial protocol complied with the recommendations of the Declaration of Helsinki and was approved by independent ethics committees for each of the participating centers.

Study Population

Men and women aged 18–75 years with T2D for at least 1 year, BMI 20.0–40.0 kg/m^2, and HbA_{1c} ≥6.5% to ≤9.5% (≥48 to ≤80 mmol/mol) were included. Patients were on NPH or insulin glargine for at least 3 months at screening (stable dose for at least 2 months before screening) alone or combined with a stable dose of metformin with/without a dipeptidyl peptidase (DPP)-4 inhibitor or a sulfonylurea. Use of insulin, other than NPH or insulin glargine, was not permitted (including rapid-acting insulins). Exclusion criteria included a clinically relevant history of gastrointestinal disease associated with prolonged nausea or vomiting or a history of unexplained/chronic pancreatitis. Patients were also excluded if they had alanine aminotransferase, amylase, or lipase more than three times the upper limit of normal (3 × ULN) or calcitonin ≥20 pg/mL.

Interventions and Concomitant Medications

DPP-4 inhibitors or sulfonylureas were discontinued at the start of the run-in period; metformin was continued at the same dose throughout the trial. During the run-in period, insulin glargine once daily was introduced (for patients previously on NPH) and/or titrated individually once weekly (for a minimum of 4 weeks up to 11 weeks) based on FPG levels according to an algorithm (4). After optimal insulin glargine titration, patients were randomized to receive lixisenatide or liraglutide if their mean self-monitored plasma glucose assessed over 1 week was <7 mmol/L (<126 mg/dL) and if they had HbA_{1c} between 6.5 and 9.0% (48 and 75 mmol/mol). After titration, insulin glargine doses were adjusted throughout the remainder of the trial to maintain FPG between 4.4 and 5.6 mmol/L (80 and 100 mg/dL). If HbA_{1c} was ≥6.5% and ≤7.5% (≥48 and ≤58 mmol/mol) on day –7, insulin glargine dose was reduced by 20% on the day before randomization (day –1) to avoid hypoglycemia when starting treatment with lixisenatide or liraglutide.

Patients randomized to receive lixisenatide were administered 10 μg once daily for 2 weeks, followed by the lixisenatide 20 μg once daily maintenance dose for the remainder of the trial. Patients randomized to receive liraglutide received 0.6 mg once daily for 1 week and then were either administered liraglutide 1.2 mg once daily until the trial end or received liraglutide 1.2 mg for 1 week before increasing their dose to 1.8 mg for the remainder of the trial. Lixisenatide or liraglutide was administered in the morning ~30 min before breakfast. Timing of

insulin glargine injections throughout the trial period was kept consistent with the patient's regimen established during the run-in period.

Pharmacodynamic Assessments

End Points

The trial primary end point was week-8 change from baseline in premeal adjusted AUC PPG from the start of a standardized breakfast (30 min after injection of the study agent) until 4 h later (AUC $PPG_{0030–0430\ h}$). Secondary end points included week-8 change from baseline in premeal adjusted glucagon and premeal adjusted C-peptide $AUC_{0030–0530\ h}$, HbA_{1c}, FPG, body weight, and 24-h (17-point) plasma glucose profiles. Gastric emptying half-life ($t_{1/2}$ – time for retention of ^{13}C to decline to 50%) and lag time (t_{lag} – time at which the percentage of ^{13}C dose excreted per unit time reaches its peak) were assessed at baseline and week 8, as were mean 24-h and day- and nighttime heart rate and diastolic (DBP) and systolic blood pressure (SBP).

Assays

Patients were outpatients except for two periods of four consecutive days for the baseline and week-8 pharmacodynamic assessments. During these periods, patients were asked to refrain from smoking and from drinking alcohol, tea, coffee, chocolate, or caffeine-containing beverages. On days –4 and 55, after an approximate 10-h overnight fast, a standardized ^{13}C-labeled breakfast (meal test 1), consisting of 281 kcal (16% protein, 62% fat, and 24% carbohydrate) and incorporating 91 mg ^{13}C-octanoic acid (Euriso-Top, Saint-Gobain, France) mixed with egg, was given to patients, and ^{13}C-octanoic acid breath tests were performed for evaluation of gastric emptying (24). In the evening, patients were given a standardized dinner (50% carbohydrate, 23% protein, 26% fat, and 676 kcal in total) and thereafter fasted for at least 8 h before eating a standardized solid breakfast (meal test 2) consisting of 451 kcal (61% carbohydrate, 12% protein, and 27% fat) for assessment of postprandial glycemic end points, glucagon, and C-peptide (days –3 and 56). On days –2 and 57 (the last days of the baseline and week-8 inpatient visits), 24-h blood pressure and heart rate monitoring were performed.

Blood samples for analysis of the primary end point were collected immediately before meal test 2 and then 10, 20, 30, 60, 90, 120, 180, and 240 min after breakfast. An additional sample was taken 30 min before meal test 2 (just before GLP-1 RA dosing at week 8) for assessment of FPG. Additional blood samples were collected for glucagon, C-peptide (11 samples), and the 24-h glucose profile (17 samples). Blood samples for HbA_{1c} assessment at screening and day –7 were stored at ambient temperature for immediate analysis; baseline (prior to first GLP-1 RA dosing) and week 4 and 8 samples were analyzed simultaneously from frozen samples (25) at study end. Plasma glucose, HbA_{1c}, glucagon, and C-peptide were assayed in a central laboratory (MLM Medical Laboratories, Mönchengladbach, Germany).

A total of 15 samples were taken for ^{13}C-octanoic acid breath testing after meal test 1 (26). Breath samples were centrally analyzed for $^{13}CO_2$ by isotope-selective nondispersive infrared spectrometry (IRIS; Analysen Technik, Bremen, Germany).

Twenty-four-hour heart rate and DBP and SBP were assessed using standard ambulatory blood pressure monitoring (model 90207; SpaceLabs, Inc., Redmond, WA). Measurements were recorded every 15 min from 0700 to 2300 h (daytime) and every 30 min from 2300 to 0700 h (nighttime).

Safety Assessments

Adverse events (AEs) were monitored throughout the trial, including symptomatic and severe hypoglycemia, increased amylase and lipase levels, and major cardiovascular events. Physical examinations, assessment of vital signs, and clinical laboratory evaluations were also performed.

In the case of amylase and/or lipase levels $>2 \times$ ULN, a retest was performed. If the retest confirmed levels $>2 \times$ ULN, this was reported as an AE. Gastroenterological evaluation and imaging were performed to complete the diagnosis if necessary.

Documented symptomatic hypoglycemia was defined as occurrence of symptoms of hypoglycemia accompanied by plasma glucose $\leq$3.9 mmol/L ($\leq$70 mg/dL). Probable symptomatic hypoglycemia was defined as symptoms of hypoglycemia without plasma glucose determination, treatable with oral carbohydrate. Severe hypoglycemia was defined as a symptomatic event requiring assistance of another person to administer carbohydrate, glucagon, or other resuscitative actions.

Statistical Methods

A sample size of 117 patients (39 study completers per treatment arm) was chosen to detect a difference of 6.7 h · mmol/L (120 h · mg/dL) in the change from baseline to week 8 in AUC $PPG_{0030–0430\ h}$ between lixisenatide 20 μg and liraglutide 1.2 or 1.8 mg, providing a power of 90%, assuming the common SD is 8.9 h · mmol/L (160 h · mg/dL), with a one-sided test overall significance level of 0.05 (using the Hochberg procedure to ensure type I error control).

Based on the results of an earlier study in patients with T2D insufficiently controlled on metformin who were treated with lixisenatide 20 μg once daily and liraglutide 1.8 mg once daily as add-on to metformin (21), a greater reduction was expected with lixisenatide 20 μg versus liraglutide 1.2 or 1.8 mg in the current study in terms of AUC $PPG_{0030–0430h}$; therefore, a one-sided approach was chosen for the primary analysis.

The modified intent-to-treat (mITT) population (all randomized patients who received at least one dose of lixisenatide/liraglutide with both a baseline and at least one postbaseline assessment of any primary or secondary variable) was used for the primary analysis. Statistical analyses were performed using SAS, version 9.2 (SAS Institute, Cary, NC). The primary end point was analyzed considering changes from baseline to week 8 and using a linear model with treatment and stratification factors (HbA_{1c} [$<$8% or $\geq$8% and $<$64 mmol/mol or $\geq$64 mmol/mol], the use of metformin, and center) as fixed effects and the baseline value of the corresponding parameter as a covariate (ANCOVA). Differences between treatment arms and CIs were estimated within the model framework. The Hochberg method was used to ensure an overall one-sided level of 5% for the comparisons between lixisenatide 20 μg versus liraglutide 1.2 mg and lixisenatide 20 μg versus liraglutide 1.8 mg. Secondary outcomes were analyzed using the same model as used for the primary outcome with a two-sided test significance level of 5%. Time course data for plasma glucose, percentage of ^{13}C excreted dose, and hourly mean heart rate were analyzed with a repeated-measures mixed model, and Dunnet adjustment procedure was used for treatment comparison with

control. Safety analyses were performed in the safety population (all randomized patients who received at least one dose of lixisenatide or liraglutide) and were based on review of descriptive statistics and potentially clinically significant abnormalities in laboratory parameters.

RESULTS

Between 22 May 2012 and 25 July 2013, 236 patients were screened and 142 patients were randomized and treated in this trial. Patient disposition is shown in Supplementary Fig. 2. Treatment discontinuations occurred in two (4.2%), three (6.4%), and one subject (2.1%) in the lixisenatide 20 μg, liraglutide 1.2 mg, and liraglutide 1.8 mg treatment arms, respectively. AE was the reason for discontinuation in four of six subjects. At screening, 77.5% of randomized patients were receiving insulin glargine as basal insulin; those who were on NPH were switched to insulin glargine at the start of the run-in period. Screening demographics and characteristics were comparable across the treatment arms (Table 1). Mean ± SD HbA_{1c} at screening was 7.8 ± 0.8% (62 ± 8 mmol/mol). Median diabetes duration ranged from 10.5 to 12.5 years (minimum 2.1, maximum 32.4 years) with a median duration of basal insulin treatment of 1.4–2.0 years (minimum 0.2, maximum 21.7 years). Mean ± SD baseline FPG at randomization was approximately 5 ± 0.9 mmol/L (94–96 mg/dL) in all treatment arms, indicating that insulin glargine titration during the run-in period was adequate.

Primary End Point

Mean ± SD AUC $PPG_{0030–0430\ h}$ with lixisenatide 20 μg declined from 15.7 ± 6.7 h · mmol/L (282.2 ± 120.9 h · mg/dL) at baseline to 3.5 ± 6.5 h · mmol/L (63.6 ± 117.9 h · mg/dL) at week 8. Mean ± SD AUC $PPG_{0030–0430\ h}$ at baseline in the liraglutide 1.2 and 1.8 mg arms was 15.6 ± 5.6 h · mmol/L (280.1 ± 99.9 h · mg/dL) and 17.0 ± 5.7 h · mmol/L (307.0 ± 103.2 h · mg/dL), respectively, and treatment resulted in reductions to 9.5 ± 5.3 h · mmol/L (171.7 ± 95.2 h · mg/dL) and 8.7 ± 3.5 h · mmol/L (156.7 ± 62.2 h · mg/dL). Marginal mean [95% one-sided CI] difference for lixisenatide 20 μg versus liraglutide 1.2 mg was −6.0 [−7.8] h · mmol/L (−108.3 [−140.0] h · mg/dL) and versus liraglutide 1.8 mg was −4.6 [−6.3] h · mmol/L (−83.0 [−114.2] h · mg/dL) ($P < 0.001$ for both comparisons). Plasma glucose profiles and change from baseline to week 8 for AUC $PPG_{0030–0430\ h}$ are shown in Fig. 1*A* and Supplementary Fig. 3.

Secondary Glycemic End Points

Twenty-four-hour plasma glucose profiles were comparable across the three treatment arms at baseline. Greatest reductions at week 8 with lixisenatide 20 μg were seen postbreakfast (up to 4 h and 30 min after injection of investigational product); after this period, plasma glucose levels were comparable versus baseline values (Fig. 1*B*). Treatment with liraglutide (1.2 and 1.8 mg) resulted in consistent glucose reductions throughout the day (Fig. 1*B*).

HbA_{1c} decreased from baseline in all treatment arms ($P < 0.001$), and mean ± SD values at trial end were comparable in the three arms: 6.2% ± 0.4% (44 ± 5 mmol/mol), 6.1% ± 0.3% (44 ± 4 mmol/mol), and 6.1% ± 0.3% (44 ± 4 mmol/mol) with lixisenatide 20 μg, liraglutide 1.2 mg, and liraglutide 1.8 mg, respectively. Reductions from baseline in HbA_{1c} were comparable for lixisenatide 20 μg and liraglutide 1.2 mg with a marginal mean treatment difference of –0.1% (95% CI –0.2, 0.03) (–0.9 mmol/mol [–2.1, 0.4]) ($P = 0.17$), while liraglutide 1.8 mg granted a marginal mean treatment difference of –0.2% (–0.3, –0.04) (–1.7 mmol/mol [–3.0, –0.5]) versus lixisenatide 20 μg ($P = 0.007$) (Table 2).

Marginal mean changes from baseline to week 8 in FPG were minimal and were comparable across the three treatment arms ($P = 0.91$ and $P = 0.90$ for lixisenatide versus liraglutide 1.2 and 1.8 mg, respectively) (Table 2).

Gastric Emptying

The percentage of the dose of ^{13}C excreted over time at baseline and week 8 for the three treatment arms is presented in Fig. 1*C*. At week 8, t_{lag} was

Table 1—Screening demographic data and patient characteristics: safety population

	Lixisenatide 20 μg (*N* = 48)	Liraglutide 1.2 mg (*N* = 47)	Liraglutide 1.8 mg (*N* = 47)
Age, years	61.6 ± 7.4	61.4 ± 7.9	62.6 ± 9.4
Male sex, *n* (%)	33 (68.8)	39 (83.0)	33 (70.2)
Caucasian patients, *n* (%)	48 (100.0)	46 (97.9)	47 (100.0)
BMI, kg/m^2	30.7 ± 4.3	30.5 ± 4.0	31.2 ± 4.3
HbA_{1c} at screening*			
%	7.8 ± 0.7	7.8 ± 0.8	7.9 ± 0.8
mmol/mol	62 ± 8	62 ± 9	62 ± 9
Current smoker, *n* (%)	4 (8.3)	11 (23.4)	10 (21.3)
Duration of T2D, years	11.4 (2.1, 32.4)	10.5 (3.9, 21.1)	12.5 (4.0, 31.6)
Duration of basal insulin treatment, years	2.0 (0.2, 21.7)	1.4 (0.2, 12.0)	1.8 (0.2, 16.7)
Patients with evening insulin glargine dosing, *n* (%)	39 (81.3)	43 (91.5)	41 (87.2)
Daily basal insulin dose at screening, units/day			
NPH	32.1 ± 18.9	23.0 ± 8.4	24.6 ± 7.8
Insulin glargine	26.9 ± 10.3	29.7 ± 13.9	31.9 ± 14.7
OAD use at screening, *n* (%)			
Any metformin use†	43 (89.6)	41 (87.2)	41 (87.2)
Metformin + DPP-4 inhibitor	9 (18.8)	9 (19.1)	5 (10.6)
Metformin + sulfonylurea	3 (6.3)	2 (4.3)	4 (8.5)

Data are means ± SD or median (minimum, maximum) unless otherwise indicated. *Stored at ambient temperature; †patients who were taking metformin alone or combined with another medication at screening.

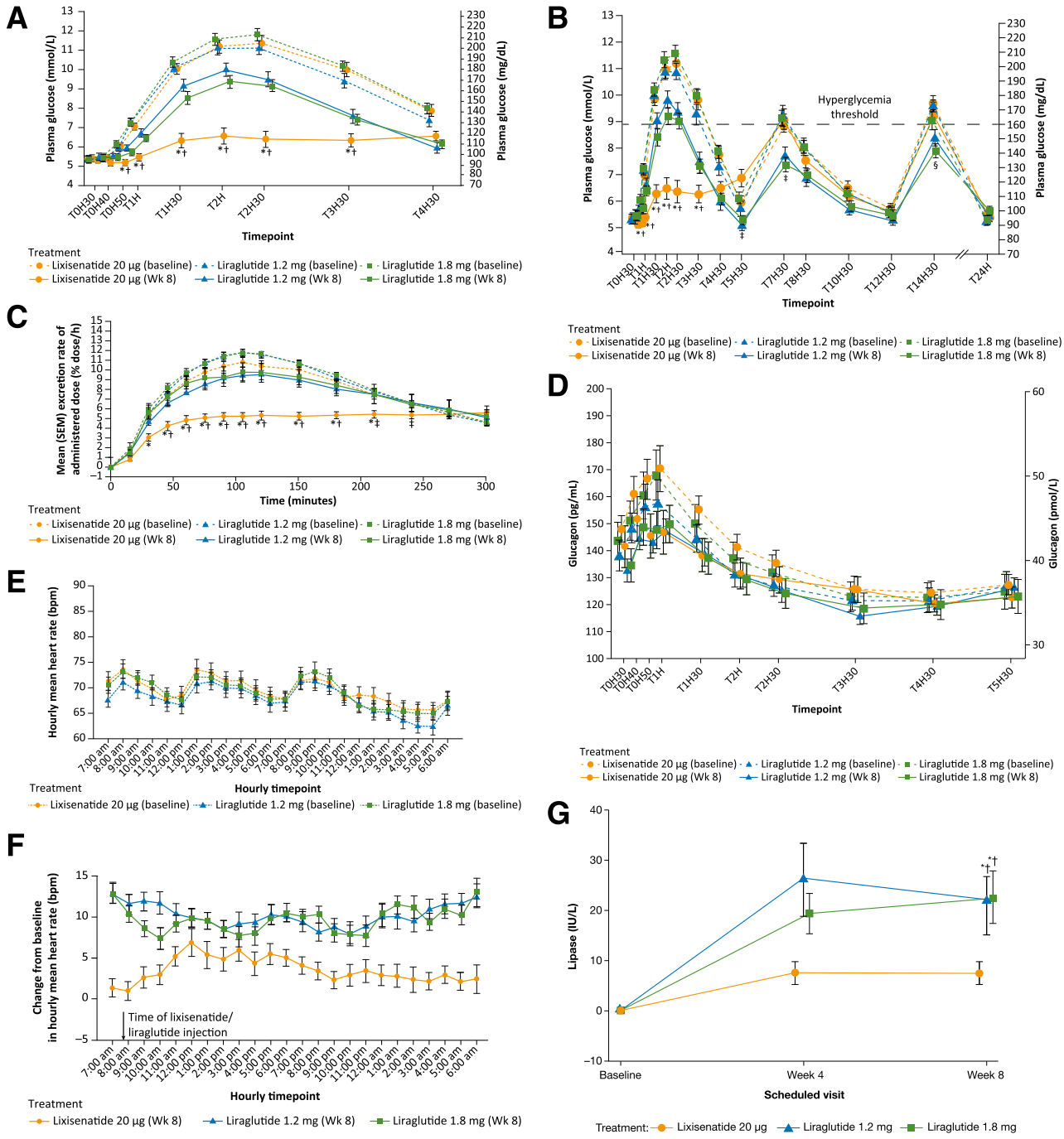

Figure 1—*A*: Mean ± SEM PPG levels at baseline and week 8 for mITT population. *$P < 0.05$ for lixisenatide 20 µg vs. liraglutide 1.2 mg; †$P < 0.05$ for lixisenatide 20 µg vs. liraglutide 1.8 mg. Statistical test compared treatment arms at each time point at week 8. *B*: Twenty-four-hour plasma glucose profiles (mean ± SEM) at baseline and week 8 for mITT population. *$P < 0.05$ for lixisenatide 20 µg vs. liraglutide 1.2 mg; †$P < 0.05$ for lixisenatide 20 µg vs. liraglutide 1.8 mg; ‡$P < 0.05$ for liraglutide 1.2 mg and 1.8 mg vs. lixisenatide 20 µg; §$P < 0.05$ for liraglutide 1.8 mg vs. lixisenatide 20 µg. Hyperglycemia threshold based on International Diabetes Federation 2011 guidelines (50). Statistical tests compared treatment arms at each time point at week 8. *C*: Percentage of the dose of ^{13}C excreted over time at baseline and week 8. *$P \leq 0.001$ vs. liraglutide 1.8 mg; †$P < 0.001$ vs. liraglutide 1.2 mg; ‡$P < 0.05$ vs. liraglutide 1.2 mg. Statistical tests compared treatment arms at each time point at week 8. *D*: Mean ± SEM glucagon concentrations at baseline and week 8 for lixisenatide and liraglutide. Statistical tests compared treatment arms at each time point at week 8. Differences between lixisenatide and liraglutide for glucagon were not significant at any time point. *E*: Baseline twenty-four-hour heart rate monitoring results (hourly mean ± SEM) for lixisenatide and liraglutide in the mITT population. *F*: Change from baseline in hourly mean heart rate (± SEM) in the mITT population. Baseline was defined as the week-1 time-matched hourly mean. *G*: Mean change from baseline (±SEM) in lipase levels in the safety population. *$P < 0.05$ for change from baseline; †$P < 0.05$ for treatment comparison vs. lixisenatide 20 µg. T0H30, 30 min after injection of the study agent; T0H40, 40 min after injection of the study agent; T0H50, 50 min after injection of the study agent; T1H, 1 h after injection of the study agent; T1H30, 1 h and 30 min after injection of the study agent; T2H, 2 h after injection of the study agent; T2H30, 2 h and 30 min after injection of the study agent; T3H30, 3 h and 30 min after injection of the study agent; T4H30, 4 h and 30 min after injection of the study agent; T5H30, 5 h and 30 min after injection of the study agent; T7H30, 7 h and 30 min after injection of the study agent; T8H30, 8 h and 30 min after injection of the study agent; T10H30, 10 h and 30 min after injection of the study agent; T12H30, 12 h and 30 min after injection of the study agent; T14H30, 14 h and 30 min after injection of the study agent; T24H, 24 h after injection of the study agent.

Table 2—Responses to therapy: mITT population

	Lixisenatide 20 μg (*N* = 46)	Liraglutide 1.2 mg (*N* = 44)	Liraglutide 1.8 mg (*N* = 46)
Premeal adjusted AUC $PPG_{0030–0430\ h}$, h · mmol/L (h · mg/dL)			
Baseline, mean ± SD	15.7 ± 6.7 (282.2 ± 120.9)	15.6 ± 5.6 (280.1 ± 99.9)	17.0 ± 5.7 (307.0 ± 103.2)
Week 8, mean ± SD	3.5 ± 6.5 (63.6 ± 117.9)	9.5 ± 5.3 (171.7 ± 95.2)	8.7 ± 3.5 (156.7 ± 62.2)
Marginal mean change ± SE	−13.3 ± 1.1 (–240.2 ± 20.0)*	−7.3 ± 1.1 (–131.8 ± 20.2)*	−8.7 ± 1.2 (–157.1 ± 21.0)*
Marginal mean (95% CI) lixi-lira difference	—	−6.0 (–7.8) (–108.3 [–140.0])‡	−4.6 (–6.3) (–83.0 [–114.2])‡
HbA_{1c}, % (mmol/mol)			
Baseline after run-in optimization, mean ± SD	6.7 ± 0.4 (50 ± 4)	6.7 ± 0.5 (50 ± 5)	6.9 ± 0.5 (51 ± 5)
Week 8, mean ± SD	6.2 ± 0.4 (44 ± 5)	6.1 ± 0.3 (44 ± 4)	6.1 ± 0.3 (44 ± 4)
Marginal mean change ± SE	−0.6 ± 0.1 (–6 ± 1)*	−0.7 ± 0.1 (–7 ± 1)*	−0.7 ± 0.1 (–8 ± 1)*
Marginal mean (95% CI) lixi-lira difference	—	−0.1 (–0.2, 0.03) (–0.9 [–2.1, 0.4])	−0.2 (–0.3, –0.04)¶ (–1.7 [–3.0, –0.5])¶
FPG, mmol/L (mg/dL)			
Baseline, mean ± SD	5.3 ± 1.0 (96.1 ± 18.6)	5.2 ± 0.8 (93.8 ± 15.1)	5.3 ± 1.0 (96.3 ± 17.9)
Week 8, mean ± SD	5.4 ± 1.0 (96.9 ± 17.7)	5.5 ± 0.9 (98.2 ± 16.7)	5.5 ± 1.1 (98.2 ± 19.7)
Marginal mean change ± SE	0.1 ± 0.2 (1.8 ± 3.9)	0.1 ± 0.2 (2.3 ± 4.0)	0.1 ± 0.2 (2.3 ± 4.1)
Marginal mean (95% CI) lixi-lira difference	—	−0.02 (–0.4, 0.4) (–0.4 [–7.8, 7.0])	−0.03 (–0.4, 0.4) (–0.5 [–7.8, 6.9])
Gastric emptying t_{lag}, min			
Baseline, mean ± SD	113.5 ± 26.5	111.2 ± 19.7	109.6 ± 20.8
Week 8, mean ± SD	258.9 ± 145.7	149.9 ± 92.2	125.2 ± 63.2
Marginal mean change ± SE	175.6 ± 23.7*	70.1 ± 23.8†	48.9 ± 24.6†
Marginal mean (95% CI) lixi-lira difference	—	105.5 (61.1, 149.9)‡	126.7 (82.8, 170.6)‡
Gastric emptying $t_{1/2}$, min			
Baseline, mean ± SD	169.5 ± 41.1	161.7 ± 23.4	164.3 ± 27.1
Week 8, mean ± SD	537.4 ± 368.7	259.2 ± 216.9	206.8 ± 138.4
Marginal mean change ± SE	453.6 ± 58.2*	175.3 ± 58.5†	130.5 ± 60.3†
Marginal mean (95% CI) lixi-lira difference	—	278.2 (168.7, 387.8)‡	323.1 (215.3, 430.9)‡
Premeal adjusted C-peptide $AUC_{0030–0530\ h}$, h · nmol/L (h · ng/mL)			
Baseline, mean ± SD	4.4 ± 2.6 (13.2 ± 7.7)	4.1 ± 1.7 (12.3 ± 5.2)	4.0 ± 1.8 (12.1 ± 5.4)
Week 8, mean ± SD	3.0 ± 3.4 (9.1 ± 10.1)	5.3 ± 2.2 (15.8 ± 6.6)	4.9 ± 2.1 (14.6 ± 6.4)
Marginal mean change ± SE	−1.2 ± 0.4 (–3.5 ± 1.1)†	1.2 ± 0.4 (3.7 ± 1.1)†	0.9 ± 0.4 (2.6 ± 1.2)†
Marginal mean (95% CI) lixi-lira difference	—	−2.4 (–3.1, –1.7) (–7.2 [–9.30, –5.1])‡	−2.0 (–2.7, –1.4) (–6.1 [–8.2, –4.1])‡
Body weight, kg			
Baseline, mean ± SD	90.3 ± 13.3	91.4 ± 14.0	93.1 ± 15.4
Week 8, mean ± SD	88.4 ± 12.9	89.3 ± 13.7	90.4 ± 15.8
Marginal mean change ± SE	−1.6 ± 0.5†	−1.8 ± 0.5†	−2.4 ± 0.5*
Marginal mean (95% CI) lixi-lira difference	—	0.2 (–0.7, 1.1)	0.8 (–0.1, 1.7)
Daily insulin glargine dose, units			
End of run-in, mean ± SD	42.5 ± 19.1	40.7 ± 18.4	44.9 ± 15.9
Day 1, mean ± SD	35.4 ± 19.0	35.0 ± 17.1	39.3 ± 15.3
Week 8, mean ± SD	37.8 ± 19.1	36.1 ± 17.8	40.9 ± 15.8
Mean change ± SD from end of run-in to week 8	−4.7 ± 4.8	−4.6 ± 6.8	−4.0 ± 6.5
Mean change ± SD from day 1 to week 8	2.4 ± 6.3	1.1 ± 3.7	1.6 ± 5.0
24-h heart rate, bpm			
Baseline, mean ± SD	70.0 ± 10.0	68.4 ± 9.8	69.8 ± 9.0
Baseline, median (min, max)	69.7 (47, 93)	66.5 (52, 92)	69.5 (53, 95)
Week 8, mean ± SD	73.7 ± 9.0	78.5 ± 9.3	79.3 ± 8.8
Week 8, median (min, max)	72.5 (57, 92)	80.7 (58, 92)	78.8 (61, 104)
Median (min, max) change at week 8	3.5 (–12, 16)	10.2 (–2, 25)	9.5 (0, 19)

Continued on p. 1269

Table 2—Continued

	Lixisenatide 20 μg (*N* = 46)	Liraglutide 1.2 mg (*N* = 44)	Liraglutide 1.8 mg (*N* = 46)
Marginal mean change ± SE at week 8	3.3 ± 1.3†	9.3 ± 1.2*	9.2 ± 1.3*
Marginal mean (95% CI) lixi-lira difference	—	6.0 (3.7, 8.2)§	5.8 (3.6, 8.0)§
24-h SBP, mmHg			
Baseline, mean ± SD	130.2 ± 11.8	130.7 ± 13.8	133.9 ± 13.9
Week 8, mean ± SD	130.6 ± 11.2	130.2 ± 12.7	131.3 ± 13.5
Mean change ± SD at week 8	0.4 ± 6.4	−0.5 ± 7.1	−2.5 ± 7.7
24-h DBP, mmHg			
Baseline, mean ± SD	72.9 ± 8.0	74.9 ± 8.8	75.6 ± 7.1
Week 8, mean ± SD	73.7 ± 7.7	77.3 ± 7.9	77.2 ± 6.8
Mean change ± SD at week 8	0.8 ± 4.1	2.4 ± 4.7	1.6 ± 4.7

Premeal adjustment was performed by subtracting premeal value from concentrations. Treatment and stratification factors (HbA_{1c} [<8% or ≥8% and <64 mmol/mol or ≥64 mmol/mol], the use of metformin [yes/no], and study site) were fixed effects in the ANCOVA used for analysis of continuous pharmacodynamic parameters; the baseline value of the corresponding parameter was the model covariate. *n* = 45 for FPG for lixisenatide 20 μg and liraglutide 1.8 mg and for C-peptide $AUC_{0030–0530\ h}$ and for glucagon $AUC_{0030–0530\ h}$ for liraglutide 1.8 mg; *n* = 43 for C-peptide $AUC_{0030–0530\ h}$ for liraglutide 1.2 mg. *n* = 42, 43, and 44 for ambulatory heart rate/blood pressure measurements in the lixisenatide 20 μg and liraglutide 1.2 and 1.8 mg arms, respectively. lixi-lira, lixisenatide-liraglutide. *$P < 0.001$, †$P < 0.05$ for change from baseline; ‡$P < 0.001$ for treatment comparison; §$P < 0.001$ for treatment comparison; ¶$P < 0.01$ for treatment comparison.

significantly longer with lixisenatide 20 μg compared with liraglutide 1.2 and 1.8 mg (mean ± SD 258.9 ± 145.7 min, 149.9 ± 92.2 min, and 125.2 ± 63.2 min, respectively; $P < 0.001$ for lixisenatide-liraglutide treatment difference) (Table 2). At week 8, $t_{1/2}$ was significantly increased in lixisenatide-treated patients versus patients treated with liraglutide 1.2 or 1.8 mg (mean ± SD 537.4 ± 368.7 min, 259.2 ± 216.9 min, and 206.8 ± 138.4 min, respectively; $P < 0.001$ for lixisenatide-liraglutide treatment difference) (Table 2).

Glucagon and C-peptide

Premeal adjusted glucagon $AUC_{0030–0530\ h}$ was similarly reduced in the three treatment arms during the first hours after meal test 2 ($P = 0.13$ and $P = 0.23$ for lixisenatide versus liraglutide 1.2 and 1.8 mg, respectively); glucagon profiles are presented in Fig. 1*D*.

Premeal adjusted C-peptide $AUC_{0030–0530\ h}$ was reduced with lixisenatide at week 8 (mean ± SD change from 4.4 ± 2.6 h · nmol/L [13.2 ± 7.7 h · ng/mL] to 3.0 ± 3.4 h · nmol/L [9.1 ± 10.1 h · ng/mL]) and increased with liraglutide 1.2 and 1.8 mg (from 4.1 ± 1.7 h · nmol/L [12.3 ± 5.2 h · ng/mL] to 5.3 ± 2.2 h · nmol/L [15.8 ± 6.6 h · ng/mL] and from 4.0 ± 1.8 h · nmol/L [12.1 ± 5.4 h · ng/mL] to 4.9 ± 2.1 h · nmol/L [14.6 ± 6.4 h · ng/mL], respectively) ($P <$ 0.001 for treatment comparison) (Table 2).

Body Weight and Insulin Dose

Mean ± SD baseline body weights in the lixisenatide and liraglutide 1.2 and 1.8 mg arms were 90.3 ± 13.3, 91.4 ± 14.0, and 93.1 ± 15.4 kg, respectively. At week 8, marginal mean ± SE changes from baseline in body weight with lixisenatide and liraglutide 1.2 mg were –1.6 ± 0.5 kg and –1.8 ± 0.5 kg, respectively ($P < 0.05$ for both) and for liraglutide 1.8 mg the change was –2.4 ± 0.5 kg ($P < 0.001$) (Table 2). Reductions from baseline in body weight were numerically greater with liraglutide 1.8 mg compared with lixisenatide, but this difference did not reach statistical significance ($P = 0.07$).

Change in insulin glargine dose was assessed from the end of the run-in titration period (day –7) and from day 1 of GLP-1 RA treatment (prior to which insulin dose was decreased by 20% if HbA_{1c} was ≤7.5% [58 mmol/mol]). No clinically relevant differences were observed between the three treatment arms in the change in insulin glargine dose from baseline to week 8 (Table 2).

Heart Rate and Blood Pressure

Twenty-four-hour heart rate at baseline was comparable in all treatment arms (Table 2). All treatments resulted in increases in heart rate from baseline ($P < 0.001$ for both liraglutide doses and $P < 0.05$ for lixisenatide). Week-8 mean ± SD 24-h heart rate was 78.5 ± 9.3 bpm and 79.3 ± 8.8 bpm for liraglutide 1.2 and 1.8 mg, respectively, compared with 73.7 ± 9.0 bpm for lixisenatide 20 μg. Week-8 marginal mean ± SE heart rate increases from baseline were 9.3 ± 1.2 bpm and 9.2 ± 1.3 bpm with liraglutide 1.2 and 1.8 mg, respectively, compared with 3.3 ± 1.3 bpm with lixisenatide 20 μg ($P < 0.001$ for treatment difference) (Table 2). Median and mean change from baseline to week-8 heart rate values were comparable within each treatment arm, indicating that heart rate increases were not influenced by outlier data (Table 2).

Greater week-8 marginal mean ± SE increases from baseline in heart rate were observed at nighttime versus daytime with liraglutide 1.2 mg (10.0 ± 1.4 bpm vs. 9.4 ± 1.3 bpm) and 1.8 mg (10.1 ± 1.5 bpm vs. 9.1 ± 1.4 bpm); this pattern was reversed with lixisenatide (nighttime increase, 2.2 ± 1.5 bpm; daytime increase, 3.7 ± 1.4 bpm) (Fig. 1*E* and *F* and Supplementary Fig. 4).

At week 8, 24-h mean ± SD DBP was slightly increased compared with baseline in patients treated with liraglutide 1.2 and 1.8 mg (2.4 ± 4.7 mmHg and 1.6 ± 4.7 mmHg, respectively) (Table 2). SBP was decreased in patients in the liraglutide 1.8 mg arm (–2.5 ± 7.7 mmHg) but remained stable in the other treatment arms (Table 2).

Safety

The most commonly reported AEs were symptomatic hypoglycemia (see below) and nausea (Supplementary Table 1). Gastrointestinal AEs were reported more frequently with liraglutide than with lixisenatide. In particular, constipation was increased with liraglutide 1.2 and 1.8 mg versus lixisenatide (5 of 47 patients

[10.6%], 3 of 47 patients [6.4%], and 0 patients, respectively). In the lixisenatide and liraglutide 1.2 and 1.8 mg groups, nausea rates were 18.8, 17.0, and 23.4%; vomiting rates were 10.4, 4.3, and 10.6%; and diarrhea rates were 6.3, 8.5, and 10.6%, respectively.

No deaths were reported in this study. Two serious AEs occurred: one event of coronary artery disease in the lixisenatide 20 μg arm (patient fully recovered after revascularization, did not discontinue lixisenatide, and completed the trial) and myocardial infarction requiring hospitalization in one patient in the liraglutide 1.2 mg arm (patient recovered after revascularization but withdrew from the trial).

Symptomatic Hypoglycemia

There were numerical differences in the number of patients experiencing symptomatic hypoglycemia (encompassing documented, probable, and severe symptomatic hypoglycemia) in the lixisenatide-treated arm compared with the liraglutide 1.2 and 1.8 mg treatment arms (14 of 48 patients [29.2%], 9 of 47 patients [19.1%], and 10 of 47 patients [21.3%], respectively, including one patient experiencing severe hypoglycemia in the lixisenatide arm) (Supplementary Table 1).

Monitoring of Pancreatic Enzymes

Treatment with liraglutide 1.2 and 1.8 mg resulted in significant lipase increases at week 8 compared with baseline ($P < 0.05$); these increases were significantly greater than reported for lixisenatide 20 μg (marginal mean ± SE increases of 21.1 ± 7.2 IU/L, 20.8 ± 7.4 IU/L, and 7.0 ± 7.1 IU/L, respectively; $P < 0.05$ for treatment comparison). These greater increases from baseline in mean lipase with either dose of liraglutide versus lixisenatide were observed from week 4 (Fig. 1*G* and Table 2). Marginal mean ± SE amylase levels showed changes from baseline at week 8 of 8.0 ± 4.0 IU/L, 5.7 ± 4.1 IU/L, and 3.0 ± 4.0 IU/L in the liraglutide 1.2 and 1.8 mg and lixisenatide 20 μg arms, respectively ($P < 0.05$ for change from baseline for liraglutide 1.2 mg, and $P = 0.17$ and $P = 0.46$ for liraglutide 1.8 mg and lixisenatide 20 μg, respectively) (Fig. 1*G* and Supplementary Table 2). No clinical signs or symptoms were associated with these pancreatic enzyme increases.

MRI showed signs of mild asymptomatic pancreatitis in a patient treated with liraglutide 1.8 mg with elevated lipase (2.2 × ULN) at day 56, confirmed by retest (2.5 × ULN); at last retest (after trial end on day 69), lipase levels in this patient decreased to 1.8 × ULN. Amylase values were within the normal range throughout the duration of the study.

CONCLUSIONS

Both lixisenatide and liraglutide in combination with optimal titration of insulin glargine (baseline FPG ~5.3 mmol/L or 95 mg/dL]) improved glycemic control to a normal HbA_{1c} of approximately 6.1–6.2% (44 mmol/mol) despite the relatively advanced T2D population in this study (median duration 10.5–12.5 years). Lixisenatide demonstrated a significantly greater effect than liraglutide (1.2 and 1.8 mg) in reducing AUC $PPG_{0030-0430\ h}$ after a standardized solid breakfast, while liraglutide had a less pronounced effect on prandial glucose levels, though this was sustained throughout the day. This difference was thought to be mainly attributable to significant delays in gastric emptying with lixisenatide compared with liraglutide, which strongly reduced postbreakfast blood glucose exposure. It has been reported previously that delayed gastric emptying with lixisenatide prolongs absorption of meal-derived glucose, resulting in blunted PPG excursions (27).

In all three treatment arms, HbA_{1c} and body weight were significantly decreased from baseline. Compared with lixisenatide 20 μg, liraglutide 1.2 mg did not show a statistical difference in terms of HbA_{1c} and body weight, while liraglutide 1.8 mg demonstrated slightly greater reductions in HbA_{1c}; however, final HbA_{1c} levels of 6.1% and 6.2% were basically similar between all treatment arms with properly optimized insulin glargine.

Safety is indeed a major issue with all new therapies and was carefully monitored in this trial. Gastrointestinal AEs of the lower intestinal tract were slightly more common with liraglutide than with lixisenatide. Symptomatic hypoglycemia occurred in more patients in the lixisenatide plus basal insulin arm in this study (29%) than in the liraglutide plus basal insulin arms (19–21%). It is possible that delay of gastric emptying by prandial lixisenatide may decrease glucose absorption to the extent that rapid recovery from hypoglycemia is prevented in some patients (28). It is, however, important to put the percentage of patients experiencing symptomatic hypoglycemia in this study into context. All randomized patients had been optimally titrated with insulin glargine, and at the start of GLP-1 RA treatment mean FPG in the lixisenatide and liraglutide arms ranged from 5.2 to 5.3 mmol/L (94 to 96 mg/dL). Moreover, titration with insulin glargine was continual throughout the trial. When patients are tightly titrated in terms of FPG or below an HbA_{1c} of 7%, increased rates of hypoglycemia are to be expected (29–31). However, despite the low FPG levels and HbA_{1c} at randomization, only one case of severe symptomatic hypoglycemia occurred in the current study; moreover, a subanalysis in patients with HbA_{1c} <7% vs. ≥ 7% revealed no difference in hypoglycemia incidence between the two groups (data not shown).

There are limited published data on the effects of GLP-1 RAs on pancreatic enzymes, especially during the early phase of treatment when changes would suggest a direct drug effect. In this trial, an increase in mean lipase levels was observed at weeks 4 and 8 in all treatment arms, with substantially greater increases in the liraglutide arms. Furthermore, one patient treated with liraglutide 1.8 mg experienced an asymptomatic episode of confirmed pancreatitis despite the short term of drug exposure. The mechanisms responsible for increases in pancreatic enzymes with GLP-1 RAs are currently unknown, and further investigation is warranted.

The results herein confirm earlier findings regarding increased heart rate with GLP-1 RAs (32,33), although this is the first study to compare the effects of prandial and nonprandial GLP-1 RAs objectively assessed by using 24-h ambulatory monitoring. Treatment with liraglutide resulted in a clinically significant increase in mean 24-h heart rate by approximately 9 bpm (compared with 3 bpm with lixisenatide). Median heart rate values at week 8 in the three treatment arms were consistent with their respective mean values, indicating that reported increases from baseline were not skewed by outlier data, although increases up to a maximum heart rate of 104 bpm were observed for liraglutide 1.8 mg. Of note, heart rate increases at week 8 with liraglutide were greater at nighttime, while heart rate increases

with lixisenatide were greatest during the day. We postulate that this difference is due to the longer half-life of liraglutide, which appeared to abolish circadian rhythms in heart rate (Fig. 1*F*) that were maintained with lixisenatide treatment. A recent pooled analysis of six 26- to 28-week phase III liraglutide studies reported overall heart rate increases of 3 bpm and significant decreases from baseline in SBP (34). As the current study was of 8 weeks' duration, it is possible that the heart rate increases reported herein may have diminished if assessed over longer periods. Alternatively, our use of 24-h ambulatory heart rate and blood pressure monitoring may have permitted more accurate assessment compared with these phase III trials. As noted by the U.S. Food and Drug Administration during evaluation of liraglutide for the treatment of obesity, a clinical pharmacology study using 24-h continuous heart rate monitoring reported increases of 5.7–6.6 bpm in 24-h heart rate and 7.0–8.9 bpm in 3-h sleeping heart rate with liraglutide 1.8 and 3 mg (35). Treatment with twice-daily prandial exenatide results in increases from baseline in heart rate (2 bpm at week 12), similar to those reported here for once daily prandial lixisenatide, and also maintains the natural circadian fluctuations in heart rate (36). The potential mechanism for increased heart rate with GLP-1 RA treatment is currently unknown and does not appear to be necessarily related to a drop in blood pressure. We postulate that heart rate increases could be ascribed to direct action at the sinus node, sympathetic stimulation, or a parasympathetic blunting effect (37), which could be extended with long-acting liraglutide. The potential clinical relevance of increased heart rate with GLP-1 RAs is also unknown, but this issue will hopefully be addressed in the ongoing prospective cardiovascular outcome trials. In the meantime, the safety/tolerability profile should be part of the decision-making process in choosing between GLP-1 RAs for treatment of T2D to lower the risk of exacerbating existing medical conditions (32).

The open-label design was a limitation of the current study, and use of double blinding would have further strengthened our results. However, as we used the approved marketed pens for administration of liraglutide, it would not have been possible to source identical placebo pens to allow blinding. In addition, this was a phase IIb study with three different treatment arms that required two- or three-step uptitration of the GLP-1 RAs under investigation and optimization of insulin glargine; the addition of placebo injections to facilitate blinding would have further complicated the study regimen. Owing to the uniformity of the study demographics, the data reported herein are only generalizable to Caucasian patients with T2D.

Combining medications with complementary effects on FPG and PPG to comprehensively manage glycemia in patients with T2D is not a novel concept. Several prandial agents have been shown to help patients with T2D achieve HbA_{1c} targets when given in combination with basal insulin (4,38–43), and treatment intensification with a rapid-acting insulin on top of basal insulin is commonly recommended for control of PPG excursions (2,44). However, more intensive insulin regimens are associated with hypoglycemia and weight gain, which can result in poor treatment acceptance and reduced compliance (45–48). In a recent study of twice daily exenatide plus insulin glargine, HbA_{1c} reductions were noninferior and FPG and body weight were significantly lower compared with mealtime bolus insulin lispro plus insulin glargine. Importantly, the rate of hypoglycemic events was reduced with exenatide versus insulin lispro (49). The GLP-1 RA class effect of weight loss and a low propensity for causing hypoglycemia make GLP-1 RAs a useful alternative to rapid-acting insulin for treatment intensification of basal insulin.

The present trial indicates that lixisenatide and liraglutide, when combined with optimized basal insulin glargine, result in robust improvements in glycemic control to levels not reached previously, albeit with differing mechanisms of action and safety/tolerability profiles. These differences should be taken into account when selecting the most appropriate treatment for a given patient. In T2D, reducing FPG with insulin glargine and targeting mealtime glucose excursions with lixisenatide is a logical and potentially valuable option in the treatment of patients with T2D inadequately controlled on basal insulin with/without OADs.

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Author Contributions. J.J.M. was involved in the clinical conduct of the study and in the writing, discussion, and review of the manuscript. J.R. was involved in the review and interpretation of data and in the writing, discussion, and review of the manuscript. A.H.-M. was responsible for medical supervision of the study as the Clinical Study Director, reviewed the data, and was involved in the writing, discussion, and review of the manuscript. C.R.-D. designed and wrote the protocol and undertook medical supervision of the study, reviewed data, and was involved in the writing, discussion, and review of the manuscript. A.D. performed the statistical analysis in the study and was involved in the writing, discussion, and review of the manuscript. H.-V.C. was involved in the writing, discussion, and review of the manuscript and was involved in the clinical conduct of the study. B.A.M. was involved in the clinical conduct of the study and in the writing, discussion, and review of the manuscript. T.F. was involved in the clinical conduct of the study and in the writing, discussion, and review

of the manuscript. C.K. was the coordinating investigator and was involved in the clinical conduct of the study and in the writing, discussion, and review of the manuscript. J.J.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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