



# Once-Daily Liraglutide Versus Lixisenatide as Add-on to Metformin in Type 2 Diabetes: A 26-Week Randomized Controlled Clinical Trial

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## OBJECTIVE

To compare the efficacy and safety of liraglutide versus lixisenatide as add-on to metformin in patients with type 2 diabetes not achieving adequate glycemic control on metformin alone.

## RESEARCH DESIGN AND METHODS

In this 26-week, randomized, parallel-group, open-label trial, 404 patients were randomized 1:1 to liraglutide 1.8 mg or lixisenatide 20  $\mu$ g as add-on to metformin. Liraglutide was administered once daily at any time of the day. Lixisenatide was administered once daily within 1 h prior to the morning or evening meal.

## RESULTS

At week 26, liraglutide reduced HbA<sub>1c</sub> (primary end point) more than lixisenatide (estimated treatment difference  $-0.62\%$  [95% CI  $-0.8$ ;  $-0.4$ ];  $P < 0.0001$ ), with more patients reaching HbA<sub>1c</sub>  $<7\%$  (53 mmol/mol) and  $\leq 6.5\%$  (48 mmol/mol) versus lixisenatide (74.2% and 54.6% for liraglutide vs. 45.5% and 26.2% for lixisenatide;  $P < 0.0001$  for both). Liraglutide reduced fasting plasma glucose more than lixisenatide (estimated treatment difference  $-1.15$  mmol/L [95% CI  $-1.5$ ;  $-0.8$ ];  $P < 0.0001$ ). Liraglutide provided greater reduction in mean 9-point self-measured plasma glucose ( $P < 0.0001$ ). However, postprandial glucose increments were smaller with lixisenatide for the meal directly after injection compared with liraglutide ( $P < 0.05$ ), with no differences between treatments across all meals. Both drugs promoted similar body weight decrease ( $-4.3$  kg for liraglutide,  $-3.7$  kg for lixisenatide;  $P = 0.23$ ). The most common adverse events in both groups were gastrointestinal disorders. Greater increases in pulse, lipase, and amylase were observed with liraglutide. Hypoglycemic episodes were rare and similar between the two treatments.

## CONCLUSIONS

At the dose levels studied, liraglutide was more effective than lixisenatide as add-on to metformin in improving glycemic control. Body weight reductions were similar. Both treatments were well tolerated, with low risk of hypoglycemia and similar gastrointestinal adverse event profiles.

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Glucagon-like peptide 1 (GLP-1) is a gut-derived incretin hormone that stimulates insulin and suppresses glucagon secretion, inhibits gastric emptying, and reduces appetite and food intake (1).

A number of GLP-1 receptor agonists (GLP-1 RAs) have been approved by health authorities and have been commercially available for the treatment of type 2 diabetes since 2005 (exenatide, liraglutide, exenatide extended release, lixisenatide, albiglutide, and dulaglutide). The current joint American Diabetes Association (ADA)/European Association for the Study of Diabetes position statement recommends the addition of a GLP-1 RA as a possible second step for treatment when glycemic control with metformin is insufficient, and GLP-1 RAs offer the advantages of body weight loss and low risk of hypoglycemia (2). GLP-1 RAs differ with respect to pharmacokinetics, pharmacodynamics (PD), timing and frequency of administration, and immunogenicity (1,3–5). Based on their half-lives and 24-h plasma coverage, they are usually categorized into short acting (half-life: 2–5 h) and long acting (half-life: 12 h to several days) (6). The half-life of liraglutide is ~13 h compared with ~3 h for lixisenatide (7,8).

Compared with native human GLP-1, liraglutide has a C16 fatty (palmitic) acid chain attached at position 26 (lysine) of the peptide, and lysine at position 34 replaced by arginine, resulting in a protracted pharmacokinetic profile suitable for once-daily administration (8). In long-term trials, as monotherapy or combined with one or two oral antidiabetes drugs, including metformin, sulfonylurea (SU), thiazolidinedione, or combined with insulin in patients with type 2 diabetes, the average decrease in HbA<sub>1c</sub> with liraglutide was up to 1.5% (9–20). In addition, improvements in fasting and postprandial plasma glucose excursions were seen with liraglutide. Liraglutide has consistently demonstrated weight reductions in clinical trials (9–20). Gastrointestinal adverse events (AEs), including transient events of nausea, diarrhea, and vomiting, were the most common AEs reported in liraglutide trials. A pulse increase of 2–3 bpm from baseline was noted with liraglutide versus placebo (9). The incidence of hypoglycemia was low, reflecting the glucose-dependent action of liraglutide. Major hypoglycemic episodes were rare, and most of these

major episodes were reported when liraglutide was used in combination with SU or insulin (9).

Lixisenatide is based on the structure of exendin-4, with ~50% homology to human GLP-1. It differs from exendin-4 by the deletion of a proline residue and addition of six lysine residues at the COOH-terminal (21). HbA<sub>1c</sub> reductions of up to 1% were observed with lixisenatide 20 µg once daily after 24 weeks' treatment in addition to oral antidiabetes drugs or basal insulin (22,23). Further, lixisenatide has a pronounced effect on postprandial plasma glucose for the meal after injection, probably due to a delay in gastric emptying. The most common side effects are nausea, vomiting, and diarrhea. Similar to other GLP-1 RAs, the risk of hypoglycemia is low except when lixisenatide is used in combination with an SU or a basal insulin (7).

The objectives of this 26-week head-to-head trial (clinicaltrials.gov reg. no. NCT01973231) were to compare liraglutide and lixisenatide as add-on to metformin with respect to glycemic control, HOMA of β-cell function (HOMA-B), weight loss, and other efficacy parameters as well as to compare the safety profile of the two drugs.

## RESEARCH DESIGN AND METHODS

### Trial Design

This was a 26-week, randomized, two-armed, open-label, active-controlled, multicenter, multinational, parallel-group trial investigating the efficacy and safety of liraglutide 1.8 mg and lixisenatide 20 µg as add-on to metformin in patients with type 2 diabetes who had not achieved adequate glycemic control on metformin (Supplementary Figure 1).

The trial was conducted from 24 October 2013 to 19 November 2014 at 56 sites in nine countries of the European Union (Czech Republic, Finland, France, Germany, Hungary, Italy, Latvia, Lithuania, and U.K.) in accordance with the Declaration of Helsinki and Good Clinical Practice (24,25). The protocol was approved by an independent ethics committee or institutional review board. Informed consent was obtained in writing prior to any trial-related activities.

### Patients

Enrolled patients were males and females with type 2 diabetes, age ≥18 years, HbA<sub>1c</sub> 7.5–10.5% (58–91 mmol/mol),

and BMI ≥20 kg/m<sup>2</sup>, who were on unchanged metformin treatment at the maximum tolerated dose (1,000 to 3,000 mg/day) for at least 90 days prior to screening.

Main exclusions included the following: female patients of child-bearing potential who was pregnant, breast-feeding, or intending to become pregnant or not using adequate contraception and patients who were previously treated with a GLP-1 RA, who were treated with glucose-lowering agents other than metformin within 90 days of screening or who had a history of chronic pancreatitis or idiopathic acute pancreatitis, a screening calcitonin value ≥50 ng/L, personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, impaired liver function (alanine aminotransferase ≥2.5 times the upper normal limit [UNL]), impaired renal function (estimated glomerular filtration rate <60 mL/min/1.73 m<sup>2</sup> per MDRD formula), or any chronic disorder or severe disease that in the opinion of the investigator might jeopardize the patient's safety or compliance with the protocol.

### Treatment

Eligible patients were randomized 1:1 using the interactive voice/web response system to receive liraglutide 1.8 mg or lixisenatide 20 µg—both combined with metformin. Liraglutide (Victoza, Novo Nordisk A/S) and lixisenatide (Lyxumia, Sanofi) were both administered once daily subcutaneously. Liraglutide was injected at any time of day irrespective of meals, but time of injection was to be consistent throughout the trial. Liraglutide was started at 0.6 mg/day, with weekly dose escalations of 0.6 mg/day until the maintenance dose of 1.8 mg/day was reached. Lixisenatide was administered within the hour prior to the first meal of the day or the evening meal in accordance with the approved label at the time of trial conduct. After a starting dose of 10 µg, the lixisenatide dose was escalated to 20 µg from day 15. If patients could not tolerate the dose of liraglutide 1.8 mg or lixisenatide 20 µg, they were to discontinue the trial product.

Patients meeting predefined hyperglycemia criteria were offered rescue treatment (suitable marketed products or attempt to further increase metformin dose) at the discretion of the investigator

as add-on to the trial product during the remainder of the trial.

### Assessments

Blood samples were drawn at specified time points and analyzed at the central laboratory (ICON Central Laboratories, Dublin, Ireland) to determine levels of HbA<sub>1c</sub>, fasting plasma glucose (FPG), endocrine pancreatic function (fasting plasma glucagon, proinsulin, C-peptide, proinsulin-to-C-peptide ratio, insulin, and HOMA-B), and fasting plasma lipid profile (triglycerides, total cholesterol, LDL, HDL, VLDL cholesterol, and free fatty acids). Patients were instructed to perform a 9-point self-measured plasma glucose (SMPG) profile (before breakfast, 90 min after the start of breakfast, before lunch, 90 min after the start of lunch, before dinner, 90 min after the start of dinner, at bedtime, at 04:00 A.M., and before breakfast the following day) within 1 week prior to site visits when the 9-point SMPG profile data were collected. Body weight, blood pressure, and pulse were measured following the standard clinical practice.

All AEs were coded using the Medical Dictionary for Regulatory Activities (version 17.1). A medical event of special interest was defined as pancreatitis or clinical suspicion of pancreatitis, malignant neoplasms, and medication errors concerning trial products. Predefined Medical Dictionary for Regulatory Activities searches were performed on all reported AEs to capture medical events of special interest. Hypoglycemic episodes were defined using the ADA classification of hypoglycemia (26) and the additional category of confirmed hypoglycemia (patients unable to treat themselves [severe hypoglycemic episode] and/or have a plasma glucose reading  $<3.1$  mmol/L [56 mg/dL]). Clinical laboratory tests included standard hematology, biochemistry, urinalysis, amylase, lipase, and calcitonin at the central laboratory. Detection of anti-drug antibodies and characterization of cross-reactivity to GLP-1 was performed at a special laboratory (Celerion Switzerland AG) with a radioimmunoassay using a radioactively labeled drug in the absence or presence of an unlabeled drug or GLP-1. Antidrug antibodies were characterized for in vitro neutralizing effect by Novo Nordisk A/S using a baby hamster kidney cell line transfected with the human GLP-1 receptor

and a reporter luciferase gene with luminescence as read out (27).

### Statistical Methods

The sample size was determined in order to demonstrate noninferiority of liraglutide versus lixisenatide as add-on to metformin with regard to change from baseline in HbA<sub>1c</sub> after 26 weeks of treatment. Based on the assumptions of a mean difference of  $-0.1\%$  for change in HbA<sub>1c</sub> for liraglutide versus lixisenatide (both as add-on to metformin), an SD of  $1.1\%$ , and a noninferiority margin of  $0.3\%$ , the sample size required in order to achieve  $90\%$  power was 160 in each arm. With an assumed dropout rate of  $20\%$ , 200 patients were needed for each arm.

The full analysis set (FAS) included all randomized patients. The safety analysis set (SAS) included all patients receiving at least one dose of any of the trial products. All efficacy end points were summarized and analyzed using the FAS, and all safety end points were summarized and analyzed using the SAS.

The statistical analyses were performed with a significance level of  $5\%$  (two-sided tests). In the primary analysis, missing values were handled by a mixed model for repeated measurements (MMRM). Data collected after initiation of rescue treatment or after discontinuation of the randomized treatment were considered missing in the primary efficacy analyses. For safety variables, all data for patients receiving rescue treatment while on randomized treatment were included.

The primary end point was the HbA<sub>1c</sub> change from baseline to week 26. HbA<sub>1c</sub> changes from baseline to measurements at 6, 12, 16, 20, and 26 weeks were analyzed using an MMRM, with the treatment and country as factors and baseline HbA<sub>1c</sub> as a covariate, all nested within week as a factor. From the MMRM model the treatment difference at week 26 was estimated and the corresponding two-sided  $95\%$  CI was calculated. Noninferiority of liraglutide versus lixisenatide was assessed by comparing the upper limit of the  $95\%$  CI for the treatment difference with the noninferiority limit of  $0.3\%$ . Similarly, superiority of liraglutide versus lixisenatide was to be concluded if the  $95\%$  CI excluded  $0\%$ .

Secondary efficacy end points, several safety end points (pulse, lipase, and amylase), and the post hoc analyses were analyzed with a method similar to that used for the primary end point. If data were log

transformed, the ratios of the means were estimated instead of the mean difference. The dichotomous end points were analyzed by a logistic regression model. Effects in the model were treatment and country as factors and baseline HbA<sub>1c</sub> as a covariate. Results are presented including the  $95\%$  CI for the odds ratio (OR) (liraglutide over lixisenatide).

Mean 9-point SMPG profile was defined as the area under the profile (calculated using the trapezoidal method) divided by the measurement time. Mean postprandial increment for all meals was calculated as the mean of the increments from before meal to 90 min after breakfast, lunch, and dinner, respectively. The four-meal increment end points derived from the 9-point SMPG profiles were analyzed with a method similar to that used for the primary end point but with three treatment groups (liraglutide-treated patients, lixisenatide-treated patients injecting in the morning, and lixisenatide-treated patients injecting in the evening).

### RESULTS

A total of 619 patients were screened, 404 patients (202 in each group) were randomized and exposed, and 340 patients (178 [88.1%] patients for liraglutide and 162 [80.2%] patients for lixisenatide) completed the 26-week treatment period without discontinuation of trial product and without rescue medication. Patient disposition is shown in Supplementary Fig. 2. Twenty-nine patients (7.2%) discontinued trial product prematurely: 13 (6.4%) for liraglutide and 16 (7.9%) for lixisenatide. More patients received rescue medication in the lixisenatide group (16 [7.9%]) compared with the liraglutide group (5 [2.5%]). All 404 patients were included in the FAS and SAS.

There were fewer females (40%) than males (60%) in the trial. Mean  $\pm$  SD age was  $56.2 \pm 10.3$  years and BMI  $34.7 \pm 6.7$  kg/m<sup>2</sup>. Mean baseline HbA<sub>1c</sub> was  $8.4 \pm 0.8\%$  ( $68 \pm 9$  mmol/mol), mean baseline FPG was  $10.4 \pm 2.3$  mmol/L ( $186.7 \pm 41.7$  mg/dL), and mean duration of diabetes was  $6.4 \pm 5.1$  years (Table 1).

#### Primary End Point: HbA<sub>1c</sub> Change From Baseline to Week 26

From weeks 0 to 26, mean HbA<sub>1c</sub> values decreased in both treatment groups but to a greater extent with liraglutide (Fig. 1A). The estimated change in HbA<sub>1c</sub> from

**Table 1—Demographic and baseline characteristics**

	Liraglutide	Lixisenatide	Total
Patients randomized (N)	202	202	404
Female; male (%)	35; 65	45; 55	40; 60
Age (years)			
Mean (SD)	56.3 (10.6)	56.1 (10.0)	56.2 (10.3)
Median (range)	57.5 (24.0; 85.0)	57.5 (23.0; 80.0)	57.5 (23.0; 85.0)
Duration of diabetes (years)			
Mean (SD)	6.5 (5.3)	6.3 (5.0)	6.4 (5.1)
Median (range)	5.4 (0.3; 33.4)	5.4 (0.3; 28.5)	5.4 (0.3; 33.4)
HbA <sub>1c</sub> (%)			
Mean (SD)	8.4 (0.7)	8.4 (0.8)	8.4 (0.8)
Median (range)	8.3 (7.0; 10.6)	8.3 (7.0; 10.5)	8.3 (7.0; 10.6)
HbA <sub>1c</sub> (mmol/mol)			
Mean (SD)	68.3 (7.9)	68.6 (8.6)	68.5 (8.2)
Median (range)	67.2 (53; 92)	67.2 (53; 91)	67.2 (53; 92)
FPG (mg/dL)			
Mean (SD)	188.7 (42.7)	184.7 (40.6)	186.7 (41.7)
Median (range)	179.3 (100.9; 367.6)	179.3 (81.1; 293.7)	179.3 (81.1; 367.6)
FPG (mmol/L)			
Mean (SD)	10.5 (2.4)	10.3 (2.3)	10.4 (2.3)
Median (range)	10.0 (5.6; 20.4)	10.0 (4.5; 16.3)	10.0 (4.5; 20.4)
Weight (kg)			
Mean (SD)	101.9 (23.3)	100.6 (19.9)	101.2 (21.7)
Median (range)	99.0 (54.6; 189.0)	98.1 (66.0; 165.7)	98.6 (54.6; 189.0)
BMI (kg/m <sup>2</sup> )			
Mean (SD)	34.5 (6.8)	34.9 (6.6)	34.7 (6.7)
Median (range)	33.7 (22.5; 58.6)	33.8 (23.8; 63.9)	33.7 (22.5; 63.9)

baseline to week 26 was  $-1.8\%$  ( $-20.0$  mmol/mol) for liraglutide and  $-1.2\%$  ( $-13.3$  mmol/mol) for lixisenatide. The estimated treatment difference was  $-0.6\%$  (95% CI  $-0.8$ ;  $-0.4$ ) ( $-6.7$  mmol/mol [ $-8.7$ ;  $-4.8$ ]);  $P < 0.0001$ . Based on the predefined noninferiority margin of 0.3%, noninferiority of liraglutide to lixisenatide was confirmed. Furthermore, as the 95% CI excluded 0, superiority of liraglutide to lixisenatide was concluded.

At week 26, a greater proportion of patients reached the HbA<sub>1c</sub> goals of  $<7\%$  (53 mmol/mol) with liraglutide (74.2%) than with lixisenatide (45.5%). The OR was 4.2 (95% CI 2.6; 6.7);  $P < 0.0001$ . Similarly, more patients achieved the HbA<sub>1c</sub>  $\leq 6.5\%$  (48 mmol/mol) target with liraglutide (54.6%) than with lixisenatide (26.2%);  $P < 0.0001$ . More patients also achieved the prespecified composite end points (HbA<sub>1c</sub>  $<7.0\%$  and no weight gain, HbA<sub>1c</sub>  $<7.0\%$  with no weight gain and no confirmed hypoglycemia, HbA<sub>1c</sub>  $<7.0\%$  with no weight gain and systolic blood pressure [SBP]  $<140$  mmHg, and HbA<sub>1c</sub> reduction  $\geq 1.0\%$  and no weight gain) with liraglutide compared with lixisenatide (Fig. 2).

#### Fasting Plasma Glucose and Nine-Point Self-measured Plasma Glucose

At week 26, FPG was reduced more with liraglutide ( $-2.9$  mmol/L [ $-51.4$  mg/dL]) than with lixisenatide ( $-1.7$  mmol/L [ $-30.6$  mg/dL]). The estimated treatment difference was  $-1.2$  mmol/L (95% CI  $-1.5$ ;  $-0.8$ ) ( $-20.8$  mg/dL [95% CI  $-27.2$ ;  $-14.4$ ]);  $P < 0.0001$  (Fig. 1B).

At week 0, the 9-point SMPG profiles for the liraglutide and lixisenatide groups were similar. After 26 weeks of treatment, the two profiles separated, with liraglutide showing lower SMPG values at most of the time points (Fig. 1D). Liraglutide provided greater reduction in the mean of 9-point SMPG compared with lixisenatide. The estimated change in the mean of 9-point SMPG from baseline to week 26 was  $-2.6$  mmol/L ( $-47.5$  mg/dL) for liraglutide and  $-1.9$  mmol/L ( $-34.0$  mg/dL) for lixisenatide. The estimated treatment difference was  $-0.8$  mmol/L (95% CI  $-1.1$ ;  $-0.4$ ) ( $-13.5$  mg/dL [95% CI  $-19.4$ ;  $-7.6$ ]);  $P < 0.0001$  (Table 2).

Four postprandial increment end points (breakfast, lunch, dinner, and mean postprandial increments across all 3 meals) from the 9-point SMPG profile

were analyzed by lixisenatide injection time (135 patients with morning injection and 45 patients with evening injection) versus all liraglutide patients. It was found that the lixisenatide morning injection group had a lower after-breakfast increment compared with liraglutide (estimated treatment difference 1.2 mmol/L [21.6 mg/dL];  $P < 0.0001$ ); the lixisenatide evening injection group had a lower after-dinner increment compared with liraglutide (estimated treatment difference 1.3 mmol/L [24.1 mg/dL];  $P = 0.0037$ ) (Table 2). However, the mean postprandial increments across all meals showed no statistically significant differences between the two treatments.

#### Body Weight

Body weight decreased from week 0 to 26 in both treatment groups (Fig. 1C). The estimated change in body weight from baseline to week 26 was  $-4.3$  kg for liraglutide and  $-3.7$  kg for lixisenatide. The estimated treatment difference was  $-0.6$  kg (95% CI  $-1.6$ ;  $0.4$ );  $P = 0.23$ .

#### Endocrine Pancreatic Function

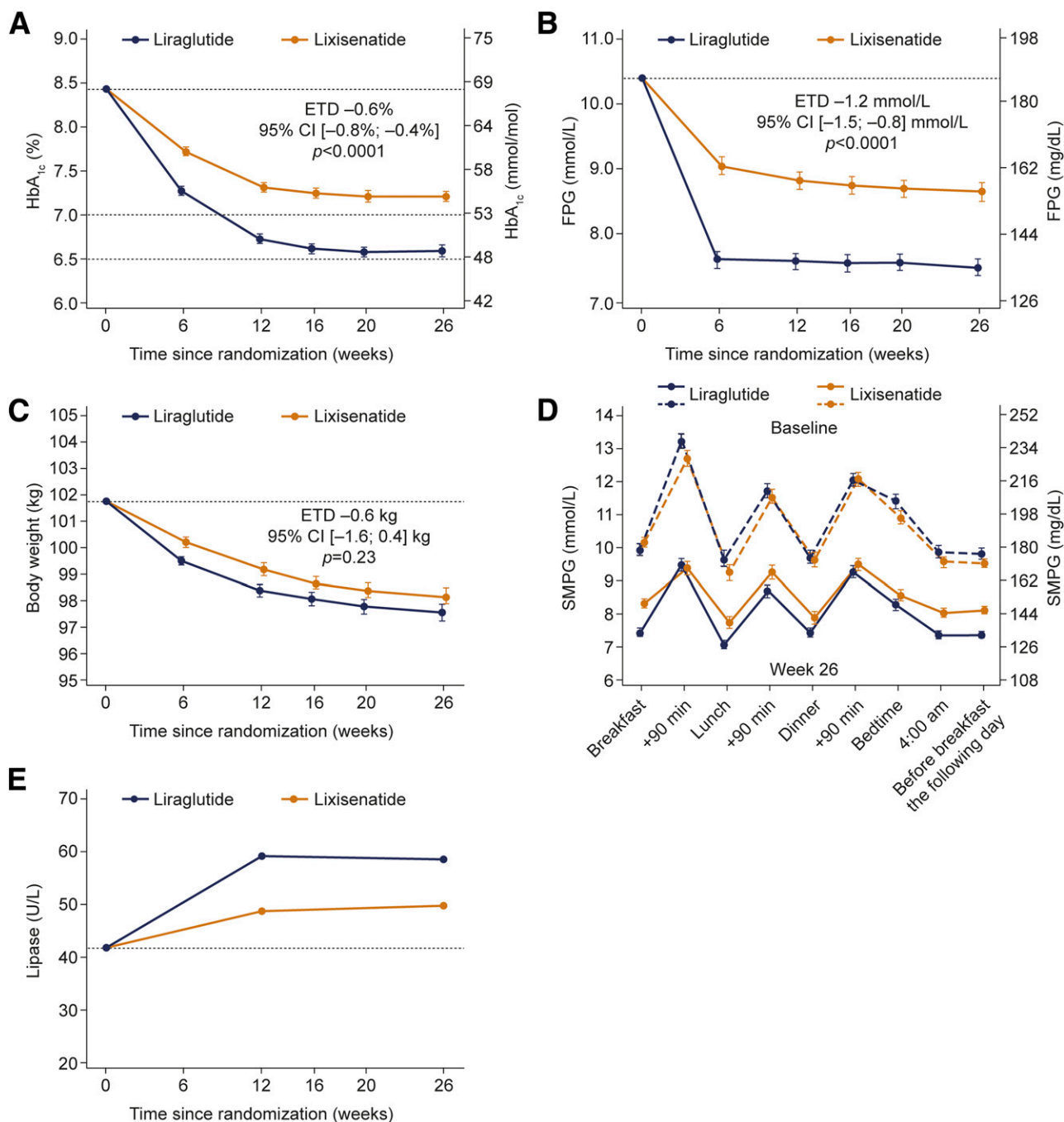
Based on the ratio to baseline, the changes in fasting state endocrine pancreatic function after 26 weeks of treatment with liraglutide or lixisenatide were in the same direction: decrease in proinsulin and proinsulin-to-C-peptide ratio, increase in C-peptide and HOMA-B, and minimal changes in fasting insulin and glucagon levels (Table 2). The results showed that after 26 weeks of treatment, liraglutide increased fasting C-peptide by 7% more and HOMA-B by 28% more than lixisenatide, and liraglutide decreased fasting proinsulin by 16% more and fasting proinsulin-to-C-peptide ratio by 22% more than lixisenatide ( $P < 0.05$  for all).

#### Lipid Profile

For the liraglutide group, HDL cholesterol was slight increased (2%) compared with baseline, and all the other lipid parameters were 4–15% decreased based on ratio to baseline (Table 2). For the lixisenatide group, slight increases for HDL (4%) and LDL (1%) were noted, whereas the rest of the lipid parameters decreased by 1–9%. There were no statistically significant differences between the two treatments.

#### Blood Pressure and Pulse

At week 26, SBP decreased to a similar extent in both treatment groups (Table 2). The estimated change in SBP from



**Figure 1**—Time course of HbA<sub>1c</sub> (A), FPG (B), body weight (C), SMPG (D), and lipase (E) from week 0 to week 26. Values are mean estimates (±SEM). These end points were analyzed using a mixed model for repeated measurements, with treatment and country as fixed factors and baseline value as covariate, all nested within visit. Group mean estimates are adjusted according to the observed baseline distribution. Normal range for lipase: 16–63 units/L. ETD, estimated treatment difference after 26 weeks.

baseline to week 26 was -4.7 mmHg for liraglutide and -3.5 mmHg for lixisenatide. The estimated treatment difference for SBP was -1.2 mmHg (95% CI -3.9; 1.5); *P* = 0.37. Diastolic blood pressure also decreased, with no difference between treatments.

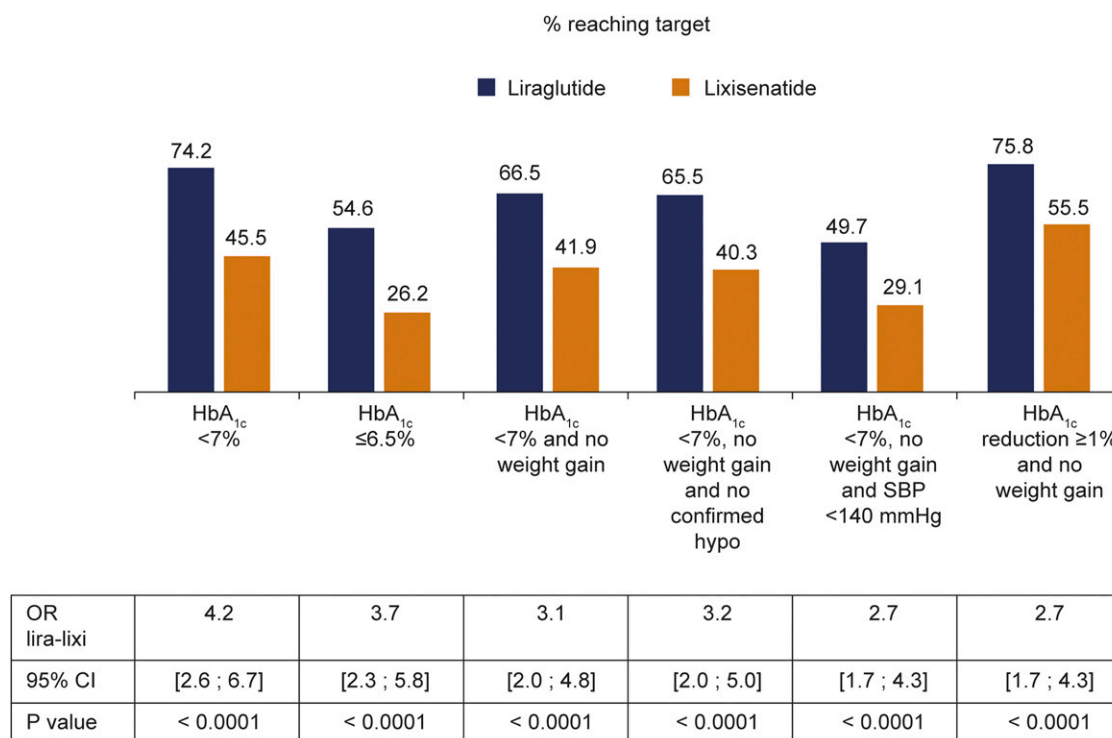
Pulse increased by 2.5 bpm with liraglutide from baseline to week 26 and

decreased by -1.1 bpm with lixisenatide. The estimated treatment difference was 3.6 bpm (95% CI 1.8; 5.4); *P* = 0.0001.

**Safety**

The proportion of patients reporting AEs was 71.8% for liraglutide and 63.9% for lixisenatide (Supplementary Table 1). Twelve patients (5.9%) reported 13 serious

AEs (SAEs) with liraglutide, and seven patients (3.5%) reported seven SAEs with lixisenatide. There was no clustering in the type of SAEs (Supplementary Table 1). The proportions of patients with AEs leading to discontinuation of trial products were similar between the two groups (liraglutide: 13 patients [6.4%]; lixisenatide: 15 patients [7.4%]). Nausea,



**Figure 2**—Percentage of patients reaching targets. Patients meeting targets (%) and estimated ORs based on a logistic regression model, with treatment and country as fixed factors and the HbA<sub>1c</sub> value at baseline as a covariate. Hypo, hypoglycemia; Lira, liraglutide; Lixi, lixisenatide.

vomiting, and abdominal distension were the most commonly reported AEs leading to discontinuation.

The most common AEs (i.e., reported by ≥5% of patients) were nausea (21.8% [liraglutide], 21.8% [lixisenatide]), diarrhea (12.4% [liraglutide], 9.9% [lixisenatide]), and vomiting (6.9% [liraglutide], 8.9% [lixisenatide]). The AEs lipase increases (8.4% [liraglutide], 2.5% [lixisenatide]) and decreased appetite (6.4% [liraglutide], 2.5% [lixisenatide]) were reported more frequently with liraglutide than with lixisenatide.

No severe hypoglycemic episodes were reported (Supplementary Table 1). Confirmed hypoglycemic episodes were rare: three patients (1.5%) with four events for liraglutide and five patients (2.5%) with eight events for lixisenatide. No differences in the rate of confirmed hypoglycemic episodes were found between the two treatment groups ( $P = 0.50$ ).

No pancreatitis or medication errors were reported in this trial. One patient treated with liraglutide (for 104 days) was diagnosed with acute myeloid leukemia, considered unlikely to be related to trial drug by the investigator.

Serum amylase and lipase levels increased from baseline to week 26 with

both treatments but to a greater extent with liraglutide (Fig. 1E and Supplementary Fig. 3). For amylase, the ratio to baseline at week 26 was 1.22 for liraglutide and 1.12 for lixisenatide. The treatment ratio (liraglutide/lixisenatide) was 1.09 (95% CI 1.03; 1.14);  $P = 0.0018$ . For lipase, the ratio to baseline at week 26 was 1.40 for liraglutide and 1.20 for lixisenatide. The treatment ratio was 1.17 (95% CI 1.07; 1.29);  $P = 0.0009$ . From the observed values at the follow-up visit (week 27, i.e., 1 week after trial product discontinuation), lipase and amylase values appeared to be regressive. A total of 27 patients (15 with liraglutide, 12 with lixisenatide) had lipase ≥ three or more times the UNL, and no patients had amylase three or more times the UNL.

At baseline 100% of patients in the liraglutide group and 99% in the lixisenatide group were anti-drug antibody negative. At week 27, two patients (1.1%) in the liraglutide group developed anti-liraglutide antibodies, and no patients developed antibodies cross-reactive to native GLP-1 or in vitro neutralizing antibodies. In the lixisenatide group, 138 patients (75.4%) were positive for anti-lixisenatide antibodies, among which one patient (0.5%) had antibodies cross-reactive to native GLP-1, and 46 patients (25.1%) had in vitro neutralizing

antibodies (Supplementary Table 2). A post hoc analysis showed that patients with neutralizing anti-lixisenatide antibodies had the smallest HbA<sub>1c</sub> reduction and therefore the greatest treatment difference versus liraglutide ( $-0.99%$  [95% CI  $-1.27$ ;  $-0.71$ ]);  $P < 0.0001$ .

## CONCLUSIONS

The joint ADA/European Association for the Study of Diabetes position statement underlines the importance of individualization of treatment targets and strategies (2). Only direct comparisons can elucidate the differences between lixisenatide and liraglutide, and such information may thus assist in the strategy for personalized treatment decisions. Previously, a 4-week PD trial (28) compared the effects of lixisenatide and liraglutide as add-on to metformin. A separate 8-week PD trial (29) compared the effects of lixisenatide and liraglutide as add-on to insulin glargine. Both trials found that lixisenatide was associated with better postprandial glucose control than liraglutide for the meal after injection (28,29). The current trial presents a 26-week head-to-head comparison of liraglutide and lixisenatide as add-on to metformin with respect to glycemic

**Table 2—Secondary end points after 26 weeks of treatment**

	Lira ( <i>n</i> = 202): change from baseline or ratio to baseline	Lixi ( <i>n</i> = 202): change from baseline or ratio to baseline	Lira-Lixi		
			ETD or ETR	95% CI	<i>P</i> *
<b>SMPG*</b>					
Mean of 9-point SMPG (mmol/L)	−2.64	−1.89	−0.75	−1.08; −0.42	<0.0001
Mean of 9-point SMPG (mg/dL)	−47.5	−34.0	−13.5	−19.4; −7.6	<0.0001
<b>Postprandial increments (mmol/L)*</b>					
All liraglutide patients ( <i>n</i> = 202) vs. lixisenatide patients injecting in the morning ( <i>n</i> = 135)					
Postbreakfast	−0.86	−2.06	1.20	0.65; 1.75	<0.0001
Postlunch	−0.60	−0.44	−0.17	−0.69; 0.35	0.53
Postdinner	−0.67	−0.39	−0.29	−0.89; 0.31	0.34
Mean of all 3 meals	−0.71	−0.94	0.22	−0.14; 0.58	0.23
All liraglutide patients ( <i>n</i> = 202) vs. lixisenatide patients injecting in the evening ( <i>n</i> = 45)					
Postbreakfast	−0.86	−0.97	0.11	−0.72; 0.94	0.80
Postlunch	−0.60	−0.47	−0.13	−0.92; 0.66	0.74
Postdinner	−0.67	−2.02	1.34	0.44; 2.25	0.0037
Mean of all 3 meals	−0.71	−1.16	0.44	−0.10; 0.99	0.11
<b>Endocrine pancreatic function†</b>					
Fasting insulin	0.95	0.92	1.03	0.91; 1.15	0.65
Fasting C-peptide	1.08	1.01	1.07	1.00; 1.15	0.04
Fasting proinsulin	0.67	0.80	0.84	0.73; 0.96	0.01
Fasting proinsulin-to-C-peptide ratio	0.62	0.80	0.78	0.71; 0.86	<0.0001
Fasting glucagon	0.97	1.00	0.97	0.92; 1.02	0.28
HOMA-B	1.67	1.30	1.28	1.14; 1.45	<0.0001
<b>Lipid profile‡</b>					
Total cholesterol	0.96	0.99	0.97	0.93; 1.00	0.08
LDL cholesterol	0.96	1.01	0.95	0.89; 1.01	0.11
VLDL cholesterol	0.87	0.92	0.95	0.88; 1.02	0.17
HDL cholesterol	1.02	1.04	0.99	0.96; 1.02	0.46
Triglycerides	0.85	0.91	0.93	0.86; 1.01	0.10
Free fatty acids	0.93	0.93	1.00	0.92; 1.09	0.92
<b>Vital signs*</b>					
SBP (mmHg)	−4.70	−3.49	−1.21	−3.87; 1.45	0.37
Diastolic blood pressure (mmHg)	−2.62	−2.69	0.07	−1.53; 1.67	0.93
Pulse (bpm)	2.50	−1.10	3.60	1.78; 5.43	0.0001

ETD, estimated treatment difference; ETR, estimated treatment ratio; HOMA-B, HOMA- $\beta$ -cell function; Lira, liraglutide; Lixi, lixisenatide. \*These end points were analyzed using mixed model for repeated measurement with visit, treatment, and country as fixed factors and baseline as a covariate, all nested within visit. Estimated change from baseline and estimated treatment difference are presented. †These end points were log transformed and then analyzed using a mixed model with treatment and country as fixed factors and log-transformed baseline value as covariate. Estimated ratio to baseline and estimated treatment ratio are presented. Postprandial increment analyses included all liraglutide-treated patients regardless of injection time (*n* = 202) and all lixisenatide patients injecting in the morning (*n* = 135) or in the evening (*n* = 45), respectively. For the remaining 22 patients, the lixisenatide injection time was unknown.

control, body weight,  $\beta$ -cell function (as measured by HOMA-B), and safety profile.

While clinically relevant HbA<sub>1c</sub> reductions were seen with both drugs in this trial, a greater HbA<sub>1c</sub> reduction was observed for liraglutide compared with lixisenatide, with an estimated treatment difference of −0.6% (95% CI −0.8; −0.4); *P* < 0.0001. Larger proportions of patients treated with liraglutide achieved the HbA<sub>1c</sub> targets of <7% and  $\leq$ 6.5%. In line with previous experience of long-acting versus short-acting GLP-1 RAs (6), the FPG reduction was greater with liraglutide than with lixisenatide. Also, the mean 9-point SMPG

profile was lower with liraglutide versus lixisenatide. Lixisenatide treatment resulted in lower postprandial glucose increments only for the meal after the drug injection compared with liraglutide (no significant differences for the mean across all meals), which is consistent with the findings from the PD trials (28,29).

Regarding any preferential reductions in postprandial glycemic increments in favor of lixisenatide (a representative of the short-acting GLP-1 RAs), this was only seen for the meal immediately after the injection (Table 2). In the current study, like with previous comparisons

of short-acting (e.g., lixisenatide) and long-acting (e.g., liraglutide) GLP-1 RAs used on a background of oral glucose-lowering agents, liraglutide was superior with respect to glycemic control (fasting and overall) (10,30–32).

In addition to the effects on glycemic control, clinically relevant body weight reductions were observed in this trial in both treatment groups, with no difference between the treatment groups.

Clinically relevant reductions in SBP and diastolic blood pressure were observed in both groups, with no differences between the groups. No marked

differences in lipid profiles were noted between the two drugs. Greater improvements in fasting C-peptide, proinsulin, proinsulin-to-C-peptide ratio, and HOMA-B were shown for liraglutide versus lixisenatide. As these parameters were, however, measured in the fasting state, the improvement was potentially partially affected by the differences in glycemic control and by the differences in drug exposure owing to different half-lives of liraglutide and lixisenatide.

Regarding safety, both liraglutide and lixisenatide were well tolerated, with similar gastrointestinal side effects already known to be associated with GLP-1 RA treatment. The most common AEs were nausea, diarrhea, and vomiting. The proportions of patients reporting AEs and SAEs, respectively, appeared comparable between the groups. No clustering of SAEs was observed in either group. Confirmed hypoglycemic episodes were rare with both treatments, and no severe hypoglycemic episodes were reported.

A pulse increase was seen in the current trial with liraglutide (2.5 bpm), the magnitude of which was in accordance with previous trials (33). Pulse decreased slightly with lixisenatide (−1.1 bpm). The time of the pulse measurement in relation to lixisenatide injection was not prespecified (i.e., depending on the time of visit, patients could have had the pulse measurement at trough concentrations of lixisenatide). In a previous study, pulse increase of 3 bpm has been described with lixisenatide compared with 9 bpm for liraglutide using 24-h monitoring (29). While the long-term cardiovascular outcome trial (CVOT) Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide) (ELIXA) (34) recently confirmed the cardiovascular safety of lixisenatide (35), results from the liraglutide CVOT Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results (LEADER) are expected to be available in 2016 (36–38).

Lipase and amylase increases have also been seen with other GLP-1 RAs and dipeptidyl peptidase-4 inhibitors (31,39,40), and therefore routine monitoring of pancreatic enzymes is implemented in trials with liraglutide. The mechanism underlying the GLP-1–mediated increase of amylase and lipase is still unclear. Increases in pancreatic enzymes were seen with both

liraglutide and lixisenatide in this trial but were higher with liraglutide. No cases of pancreatitis occurred in the present trial, and the clinical relevance of these observations is uncertain.

A low incidence of anti-drug antibody development was seen with liraglutide (two patients [1.1%]) compared with lixisenatide (138 patients [75.4%]). While HbA<sub>1c</sub> did not seem to be impacted by anti-drug antibody status overall, the subgroup of patients with neutralizing antibodies to lixisenatide seemed to have the least HbA<sub>1c</sub> reduction (post hoc analysis).

Potential limitations of this trial include the relatively short 6-month duration, open-label nature, and impossibility of a double-dummy design. We did not study the effect of liraglutide 1.2 mg versus lixisenatide in the current trial. In previous trials (11,15) using both doses of liraglutide as add-on to metformin, minor differences in HbA<sub>1c</sub> reduction were observed between 1.8 mg and 1.2 mg. Therefore the estimated treatment difference of liraglutide 1.2 mg versus lixisenatide would most likely be similar to that between liraglutide 1.8 mg and lixisenatide.

In conclusion, at the dose levels studied, liraglutide was more effective than lixisenatide as add-on to metformin in improving glycemic control. Body weight reductions were similar. Both treatments were well tolerated, with low risk of hypoglycemia and similar gastrointestinal adverse events profiles; however, increases in pulse, lipase, and amylase were greater for liraglutide.

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GlaxoSmithKline, Janssen Pharmaceutical Companies of Johnson & Johnson, Merck Sharp & Dohme, and Sanofi Pasteur SA. M.R. served on advisory panels for AstraZeneca Pharmaceuticals LP, Eli Lilly and Company/Boehringer Ingelheim Pharmaceuticals, Inc., Kowa Pharmaceuticals, and Novo Nordisk, Inc.; on the speaker's bureau for AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim Pharmaceuticals, Inc., Merck Sharp & Dohme, and Novo Nordisk, Inc.; and has participated in conferences sponsored by Eli Lilly and Company, Novartis Pharma GmbH, Novo Nordisk, Inc., and Servier. A.J. served on advisory panels for Novo Nordisk and Sanofi and performs commercial research, which is undertaken on behalf of the North Bristol NHS Trust, for Janssen, AstraZeneca, Eli Lilly, Novo Nordisk, Bayer, and Sanofi. H.B.-T. and J.M. are Novo Nordisk employees. B.C. has served as a board member for Amgen Inc., AstraZeneca/Bristol-Myers Squibb, Eli Lilly and Company, Janssen Pharmaceutical Companies of Johnson & Johnson, Novo Nordisk A/S, Regeneron Pharmaceuticals, Inc., Sanofi Pasteur SA, and Takeda Pharmaceutical Company and as a consultant for Genfit. No other potential conflicts of interest relevant to this article were reported.

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