



Glucagon-Like Peptide 1 Receptor Agonist or Bolus Insulin With Optimized Basal Insulin in Type 2 Diabetes

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OBJECTIVE

Mealtime insulin is commonly added to manage hyperglycemia in type 2 diabetes when basal insulin is insufficient. However, this complex regimen is associated with weight gain and hypoglycemia. This study compared the efficacy and safety of exenatide twice daily or mealtime insulin lispro in patients inadequately controlled by insulin glargine and metformin despite up-titration.

RESEARCH DESIGN AND METHODS

In this 30-week, open-label, multicenter, randomized, noninferiority trial with 12 weeks prior insulin optimization, 627 patients with insufficient postoptimization glycated hemoglobin A_{1c} (HbA_{1c}) were randomized to exenatide (10–20 μg/day) or thrice-daily mealtime lispro titrated to premeal glucose of 5.6–6.0 mmol/L, both added to insulin glargine (mean 61 units/day at randomization) and metformin (mean 2,000 mg/day).

RESULTS

Randomization HbA_{1c} and fasting glucose (FG) were 8.3% (67 mmol/mol) and 7.1 mmol/L for exenatide and 8.2% (66 mmol/mol) and 7.1 mmol/L for lispro. At 30 weeks postrandomization, mean HbA_{1c} changes were noninferior for exenatide compared with lispro (–1.13 and –1.10%, respectively); treatment differences were –0.04 (95% CI –0.18, 0.11) in per-protocol ($n = 510$) and –0.03 (95% CI –0.16, 0.11) in intent-to-treat ($n = 627$) populations. FG was lower with exenatide than lispro (6.5 vs. 7.2 mmol/L; $P = 0.002$). Weight decreased with exenatide and increased with lispro (–2.5 vs. +2.1 kg; $P < 0.001$). More patients reported treatment satisfaction and better quality of life with exenatide than lispro, although a larger proportion of patients with exenatide experienced treatment-emergent adverse events. Exenatide resulted in fewer nonnocturnal hypoglycemic episodes but more gastrointestinal adverse events than lispro.

CONCLUSIONS

Adding exenatide to titrated glargine with metformin resulted in similar glycemic control as adding lispro and was well tolerated. These findings support exenatide as a noninsulin addition for patients failing basal insulin.

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A slide set summarizing this article is available online.

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Type 2 diabetes is a progressive disease requiring treatment intensification to maintain glycemic control (1,2). For patients unable to achieve individualized glycemic targets with oral glucose-lowering agents, basal insulin is usually initiated and uptitrated to a fasting glucose (FG) target, but postprandial glucose may remain elevated. Although mealtime insulin may control postprandial glucose (1), weight gain, increased hypoglycemia risk, and poor patient acceptance may result (1). Recent studies suggest that adding a short-acting glucagon-like peptide 1 (GLP-1) receptor agonist to target postprandial glucose may be a viable option, but, to date, no studies directly compared the efficacy and safety of a GLP-1 receptor agonist with mealtime insulin in patients receiving optimized basal insulin (3,4). Placebo-controlled studies have been criticized for providing insufficient data for translation into clinical practice (5).

We prospectively compared glycated hemoglobin A_{1c} (HbA_{1c}) and other outcomes over 30 weeks between the short-acting GLP-1 receptor agonist exenatide twice daily (exenatide) and titrated mealtime insulin lispro (lispro), both added to titrated insulin glargine (glargine) in metformin-treated patients with insufficient glycemic control despite 12 weeks of intensive protocol-based glargine titration.

RESEARCH DESIGN AND METHODS

Study Design and Patients

This open-label, randomized, controlled, noninferiority study (NCT00960661) was conducted at 108 centers in 17 countries between September 2009 and August 2012. The 44-week study included a 2-week screening period, 12-week basal insulin optimization (BIO) phase, and 30-week intervention phase. Enrolled patients were males and females 18 years and older with type 2 diabetes treated with insulin glargine and metformin \pm sulfonylurea with HbA_{1c} of 7.0% (53 mmol/mol) to 10.0% (86 mmol/mol) and BMI of 25.0 kg/m² (23.0 for South Korean participants) to 45.0 kg/m². Exclusion criteria included use of other glucose-lowering agents and/or clinical history, condition, or concomitant medication that could confound efficacy or safety (Supplementary Table 1). At entry, patients continued metformin and discontinued sulfonylurea. Bedtime glargine

was titrated to FG of 5.6 mmol/L or lower without hypoglycemia (i.e., glucose <3.0 mmol/L) (6), based on self-monitored blood glucose (International Federation of Clinical Chemistry and Laboratory Medicine plasma-equivalent referent meters; Roche Diagnostics, Indianapolis, IN) and dosing aid (Supplementary Fig. 1). The BIO-phase identified patients requiring additional therapy by failure to reach HbA_{1c} 7.0% (53 mmol/mol) or less on titrated basal insulin and metformin.

All patients provided prior written informed consent. The protocol was approved by ethics and regulatory committees and institutional review boards in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Randomization

Patients were allocated 1:1 to treatment groups using block randomization with computer-generated random sequence stratified by country and prior sulfonylurea use.

Procedures

At randomization (defined as 0 weeks), daily glargine was reduced 10% or more in patients allocated to exenatide with HbA_{1c} of 8.0% (64 mmol/mol) or less. In a prior study comparing addition of exenatide twice a day or placebo to insulin glargine, reduction of glargine by 20% in patients with HbA_{1c} of 8.0% or less was associated with a low risk of major hypoglycemia; however, there was no clear evidence that a reduction of this magnitude was necessary to reduce hypoglycemia risk. A more conservative approach of a 10% reduction was taken in this study (3). Patients were instructed to inject exenatide twice daily before the two largest meals, with at least 6 h between dosing. Regimen was 5 μ g twice daily per injection for the first 4 weeks and 10 μ g per injection thereafter. Exenatide dose reduction was allowed based on tolerability.

Patients randomized to lispro reduced daily glargine by one-half or one-third, at the investigator's discretion. In previous studies that added mealtime lispro to glargine, reductions by one-half were associated with a low incidence of severe hypoglycemia (7,8). The reduced amount was replaced with three doses of lispro injected before meals to maintain the same total insulin dose. Thereafter, glargine was titrated as in the BIO-phase

(Supplementary Fig. 1) (6), and lispro was titrated based on self-monitored premeal glucose values (Supplementary Fig. 2) (7).

The recommended insulin titration algorithms were prospectively planned, aiming to assure consistent insulin titration across multiple sites and countries involved in the study. Patients were contacted once weekly in person or by telephone for the first 8 weeks after randomization and biweekly thereafter. Participants were asked to monitor FG levels daily (6,7), perform a four-point self-monitoring glucose profile twice weekly (before breakfast, lunch, dinner, and bedtime), and perform a seven-point self-monitoring glucose profile within 2 weeks of scheduled visits. Patient compliance was assessed by the investigators or their designee at each visit based on a review of glycemic control, adherence to visit schedule, completion of study diaries, and regular study drug use. Noncompliant patients received education and training as required; consistently noncompliant patients could be discontinued from the study. Nevertheless, no specific study data were collected for analysis of treatment compliance and therefore were not reported separately.

Anthropometric characteristics, blood pressure, and heart rate were measured while fasting at baseline, randomization, and follow-up visits. Patient-reported outcome assessments included Impact of Weight on Quality of Life (IWQOL) questionnaire (short form) (9) and Diabetes Treatment Satisfaction Questionnaire (DTSQ) status or change version (10,11) with measurements at baseline, randomization, week 8, and end point. Samples were collected at all visits for HbA_{1c} and fasting serum glucose. Fasting samples were collected at weeks 0 and 30 for lipids and exploratory biomarkers (Quintiles Central Laboratories, Marietta, GA). Anti-exenatide antibodies (12) were measured at weeks 0, 8, and 30 (Millipore Corp., St. Charles, MO). High antibody positivity was defined as a titer \geq 1/625.

Primary outcome was change from randomization to 30 weeks in HbA_{1c}. Secondary outcomes included weight, percentage of patients achieving HbA_{1c} targets with weight gain of 1 kg or less, HbA_{1c} of 6.5% (48 mmol/mol) or less or 7.0% (53 mmol/mol) or less, FG, seven-point self-monitored blood glucose profiles, insulin dose, blood pressure,

and lipid measurements. Exploratory biomarkers included 1,5-anhydroglucitol, adiponectin, hs-CRP, and urine albumin/creatinine. Safety measures included hypoglycemic events (Supplementary Table 2) and adverse events.

Statistical Analyses

The primary objective of the study was to compare the difference in HbA_{1c} change from randomization to 30 weeks between exenatide or lispro added to glargine in the per-protocol (PP) population. Noninferiority was assessed using an HbA_{1c} margin of 0.4%. If this objective was met, a second noninferiority comparison would be conducted with an HbA_{1c} margin of 0.3%. If noninferiority was established using this stricter margin, superiority would be tested in the intent-to-treat (ITT) population. Due to the ordered nature of objectives, no adjustment to significance level was required to maintain the study-wise significance level. Significance testing was conducted at the two-sided 5% level.

A PP population of 464 patients was calculated to provide 96% power to conclude noninferiority between the treatments in change from randomization HbA_{1c} assuming that there was no difference and the SD was 1.15%. This sample size would provide 80% power to conclude noninferiority with a margin of 0.3%. Based on previous studies (3,13), it was assumed that 20% of randomized patients would be excluded from the PP analysis; therefore, 580 randomized patients were required.

The primary noninferiority objective was assessed using the PP population, as ITT analyses of noninferiority are prone to increased chance of incorrectly concluding noninferiority when one treatment is actually inferior. The PP population was defined as all randomized patients who completed the study and had no violation of the inclusion/exclusion/discontinuation criteria. As supportive evidence, the primary analysis was repeated using the ITT analysis set, i.e., all randomized subjects receiving at least one dose of study drug grouped according to randomized treatment, regardless of the study drug actually received. Secondary analyses were conducted in the PP population. Exploratory end points and post hoc subgroup analyses were conducted using

the ITT population. Safety analyses were conducted on the as-treated analysis set, i.e., all randomized subjects taking at least one dose of study drug according to the treatment received. The ITT and as-treated populations were identical.

Mixed models for repeated measures (MMRM) were used for the primary analysis with baseline HbA_{1c}, country, prior use of sulfonylureas, randomized treatment, visit, and treatment-by-visit interaction as fixed effects. Noninferiority was concluded if the upper bound of the 95% CI for the treatment contrast at week 30 excluded the corresponding noninferiority margin. ANCOVA analyses using last observation carried forward were also conducted on PP and ITT populations. The proportion of patients achieving glycemic targets were analyzed using logistic regression models with baseline HbA_{1c}, prior use of sulfonylureas, and country as fixed effects. Variables measured twice (e.g., lipids) were analyzed with an ANCOVA model. The proportion of patients with one or more hypoglycemic episodes was compared using Fisher exact test. All treatment comparisons used a two-sided 5% significance level.

RESULTS

Study Population

Of 1,036 patients screened, 917 entered the 12-week BIO-phase (Fig. 1) during which mean HbA_{1c} decreased from 8.5% (69 mmol/mol) to 8.2% (66 mmol/mol) and FG from 8.4 to 7.2 mmol/L (Table 1). At week 12, 92 patients achieved HbA_{1c} of 7% (53 mmol/mol) or less, with HbA_{1c} decreasing from 7.9% (63 mmol/mol) to 6.7% (50 mmol/mol) and FG from 7.1 to 5.9 mmol/L; 173 patients withdrew for reasons specified in Fig. 1. Despite up-titration of glargine, HbA_{1c} decreased from 8.6% (70 mmol/mol) to 8.4% (68 mmol/mol) and FG from 8.6 to 7.3 mmol/L in 652 patients. Of these eligible patients, 637 were randomized to add exenatide or lispro to titrated glargine and 627 patients continued in the study; 36.2% had used sulfonylureas prior to enrollment in the BIO-phase. Characteristics at randomization were similar between arms (Table 2). Randomized patients had a mean age of 59.8 years, median diabetes duration of 12 years, and mean HbA_{1c} of 8.2% (66 mmol/mol). The majority were

Caucasian and overweight (Table 2). Discontinuation rates were comparable for exenatide (316 ITT; 247 PP) and lispro (321 ITT; 263 PP) (Fig. 1).

Primary Outcome

The difference in HbA_{1c} change from randomization to end point at 30 weeks between exenatide or lispro added to glargine was -0.04 (95% CI $-0.18, 0.11$) in the PP population. The upper limit of the 95% CI for the treatment difference was <0.4 and $<0.3\%$, demonstrating noninferiority. Changes from randomization in HbA_{1c} with the addition of exenatide or lispro to glargine were -1.13 (12.4 mmol/mol) (95% CI $-1.24, -1.03$) and -1.10 (12.0 mmol/mol) (95% CI $-1.20, -1.00$) ($P = 0.627$), respectively (Table 2 and Fig. 2A). In the ITT population, the difference in change in HbA_{1c} from randomization to end point between exenatide or lispro added to glargine was -0.03 (95% CI $-0.16, 0.11$). Changes from randomization in HbA_{1c} with added exenatide or lispro were -1.10 (95% CI $-1.20, -1.00$) and -1.07 ($-1.17, -0.97$) ($P = 0.702$), respectively (Fig. 2B and Supplementary Table 3).

Secondary Outcomes

Proportions of patients with HbA_{1c} $\leq 7.0\%$ (53 mmol/mol) or 6.5% (48 mmol/mol) were similar (Table 2). Achievement of composite HbA_{1c} and weight targets favored exenatide ($P < 0.001$) (Table 2). FG decreased with exenatide ($P = 0.002$) (Fig. 2C). Changes in postprandial glucose were similar except after lunch ($P < 0.001$) (Table 2 and Fig. 2D). After 30 weeks, average weight had decreased with exenatide and increased with lispro ($P < 0.001$) (Table 2 and Fig. 2F). No significant between-group differences were noted for fasting glucagon or total cholesterol, LDL cholesterol, or triglycerides; however, a between-group difference for HDL cholesterol was noted (Table 2).

At study end, mean glargine dose had decreased somewhat in both groups (Table 2 and Fig. 2E), while the mean glargine dose was 56.8 units in the exenatide group and 51.5 units in the lispro group ($P < 0.001$). In patients receiving exenatide, 73.3% administered 10 μg per injection and 11.1% administered 5 μg per injection. Insulin titration deviations for glargine dosing were 81.4% in the exenatide arm and 80.2% in the lispro arm.

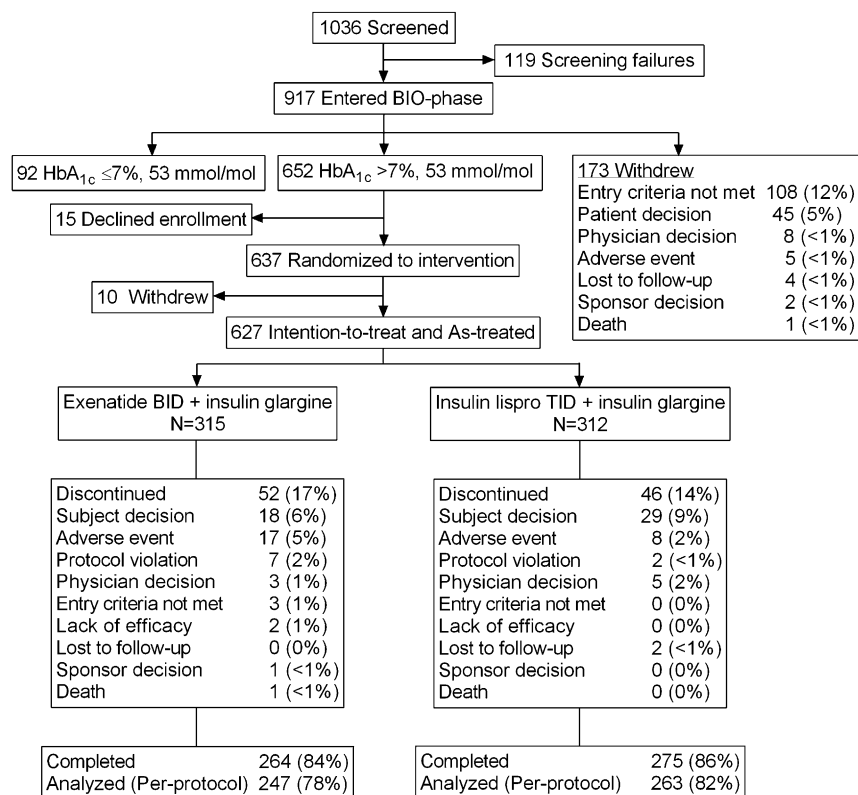


Figure 1—Enrollment and outcomes.

Systolic blood pressure decreased with exenatide (between-group difference, $P < 0.001$), whereas no between-group differences were noted for diastolic blood pressure or pulse rate (Table 2). No between-group differences were noted for hs-CRP, adiponectin, 1,5-anhydroglucitol, or urine albumin/creatinine (Table 2).

Both exenatide and lispro recipients reported significant improvements in overall perceived treatment satisfaction (DTSQ) and perceived frequency of “high blood sugar” compared with baseline (start of BIO-phase); improvements were greater with exenatide ($P = 0.003$) (Supplementary Table 5). More “low blood sugar” was perceived for lispro than exenatide. On the DTSQ, average scores for both exenatide and lispro at end point indicated high levels of treatment satisfaction. In addition, exenatide recipients reported significant ($P < 0.001$) improvement in perceived impact of weight on quality of life (IWQOL total score) from randomization, whereas lispro recipients did not ($P = 0.037$ between groups).

Safety and Tolerability

Overall, 70 (22%) exenatide patients tested positive for anti-exenatide antibodies

at study end; of these, 10 had high-titer antibodies (Supplementary Fig. 4) (12). In patient subpopulations determined by antibody status, antibody positivity was associated with similar HbA_{1c} changes (Supplementary Table 5) and incidences of treatment-emergent adverse events (74.3 vs. 72.2%, respectively).

The proportion of patients experiencing treatment-emergent adverse events was greater for exenatide than lispro (Supplementary Table 4). Gastrointestinal-related adverse events, including nausea, vomiting, and diarrhea, were more common for exenatide (47 vs. 13% for lispro) (Supplementary Table 4). Incidence of hypoglycemia was greater with lispro for minor (41 vs. 30% for exenatide) and confirmed nonnocturnal hypoglycemia (34 vs. 15% for exenatide) (Supplementary Table 4). Two exenatide and seven lispro recipients had at least one major hypoglycemic episode. Nocturnal hypoglycemia was similar for exenatide and lispro (25 vs. 27%, respectively).

One patient died before randomization from multiple organ failure. In the exenatide arm, one patient died of

hemorrhagic stroke, and one patient (treated with exenatide for 71 days) was diagnosed with pancreatic cancer, discontinued exenatide and the study, and died 1.5 years poststudy. No other cancers were observed in either arm. The percentage of patients with serious adverse events was similar between groups (5.7% for exenatide and 7.4% for lispro). No pancreatitis was observed. One exenatide-treated patient was hospitalized for acute renal failure and recovered.

CONCLUSIONS

For patients with advanced type 2 diabetes unable to achieve glycemic control despite titrated basal insulin titration over 12 weeks (6,14), adding the short-acting GLP-1 receptor agonist exenatide before the two largest meals improved glycemic control similarly to mealtime (thrice daily) lispro. Additionally, exenatide was associated with lower FG, less nonnocturnal hypoglycemia, weight loss, reduced systolic blood pressure, and better quality of life. More adverse events, mainly gastrointestinal, were observed with exenatide than lispro. To date, available studies combining a GLP-1 receptor agonist with basal insulin used placebo as a comparator and failed to first optimize FG and identify patients needing additional therapy targeting postprandial hyperglycemia (3,4,13,15). By directly comparing a short-acting GLP-1 receptor agonist added to titrated basal insulin with a standard basal-bolus insulin regimen (1), this study provides clinically relevant data on the benefits and risks of this strategy.

Greater FG reduction was observed for exenatide versus lispro despite similar HbA_{1c} changes at end point. Although both groups had comparable FG and daily glargine doses after the initial 12-week glargine titration period, glargine dose was reduced more aggressively at randomization in the lispro group to allow initiation of thrice-daily mealtime insulin. Even though the glargine was titrated according to the protocol, the possibility still remains that the lower dosage of glargine in the lispro group at study end could have affected the primary outcome. This strategy may have resulted in the lower doses of glargine with lispro at study end, although in both groups a similar titration algorithm for insulin glargine was used, which also was used in the BIO-phase. Interestingly,

Table 1—Baseline and end of BIO-phase characteristics of the study population

Characteristic	Enrolled (n = 917)	Responders (n = 92)	Failures (n = 652)
Demographic			
Men	457 (50%)	56 (61%)	315 (48%)
Age (years), mean (SD)	59.8 (9.5)	57.4 (8.9)	59.7 (9.4)
Duration of diabetes (years), median (IQR)	12 (8–16)	10 (6–14)	12 (8–16)
Ethnic origin			
White	809 (88%)	79 (86%)	568 (87%)
Asian	49 (5%)	5 (5%)	37 (6%)
African American	5 (<1%)	0 (0%)	3 (<1%)
Other*	53 (6%)	8 (9%)	43 (7%)
Clinical			
Use of glucose-lowering medication			
Metformin daily dose (mg), mean (SD)	2,027 (655)	2,037 (703)	2,010 (648)
Insulin glargine (units/day), mean (SD) [†]			
Start of BIO-phase	40.7 (24.2)	34.5 (17.0)	40.6 (24.2)
End of BIO-phase	56.8 (30.5)	47.3 (22.2)	58.0 (31.0)
Insulin glargine (units/day), median (IQR) [†]			
Start of BIO-phase	34 (24–46)	30 (24–40)	34 (25–46)
End of BIO-phase	48 (38–70)	41 (31–56)	50 (38–70)
Glycemic measures			
HbA _{1c} (%) [mmol/mol], mean (SD)			
Start of BIO-phase	8.5 (1.0) [69 (10.9)]	7.9 (0.7) [63 (7.7)]	8.6 (0.8) [70 (8.7)]
End of BIO-phase	8.2 (1.0) [66 (10.9)]	6.7 (0.4) [50 (4.4)]	8.4 (0.9) [68 (9.8)]
FG (mmol/L), mean (SD)			
Start of BIO-phase	8.4 (2.8)	7.1 (2.2)	8.6 (2.8)
End of BIO-phase	7.2 (2.4)	5.9 (1.7)	7.3 (2.4)
Anthropometric measures			
Body weight (kg), mean (SD)			
Start of BIO-phase	88.9 (17.4)	89.4 (18.1)	88.9 (16.9)
End of BIO-phase	89.3 (17.1)	90.1 (17.5)	89.3 (17.0)
BMI (kg/m ²), mean (SD)			
Start of BIO-phase	32.1 (5.0)	31.8 (4.7)	32.2 (4.8)
End of BIO-phase	32.3 (4.8)	31.5 (4.5)	32.3 (4.8)
Blood pressure (mmHg), mean (SD)			
Systolic			
Start of BIO-phase	138 (16)	137 (18)	137 (15)
End of BIO-phase	—	—	—
Diastolic			
Start of BIO-phase	80 (10)	80 (10)	79 (10)
End of BIO-phase	—	—	—
Pulse rate (beats per min), mean (SD)			
Start of BIO-phase	76 (11)	77 (11)	75 (11)
End of BIO-phase	—	—	—

Enrolled, patients who enrolled in the BIO-phase; responders, patients at the end of the BIO-phase who had HbA_{1c} of 7% or less after 12 weeks of titrated insulin glargine; failures, patients at the end of the BIO-phase who had HbA_{1c} >7% and who were eligible to enroll in the intervention phase of the study. *American Indian or Native Alaskan. [†]As-treated population.

the between-group difference in FG disappeared in the subset of patients with confirmed nocturnal hypoglycemia (data not shown), suggesting that glargine dose titration was guided by clinical symptoms rather than by FG values. Additionally, fasting glucagon does not explain the FG difference since glucagon concentrations tended to be higher with exenatide, predictive of increased hepatic glucose output (16,17). The intrinsic ability of short-acting GLP-1 receptor agonists to lower FG concentrations via effects on insulin secretion and/or glucagon suppression

(18–22), which differs from the short-acting insulins such as lispro, may provide the best explanation of the FG difference. Nevertheless, it remains unclear whether exenatide's stronger effects on FG compared with lispro are due to clinical factors such as titration practices or to physiological differences in response to therapy.

Control of postmeal glycemic excursions was generally similar for both treatments, with the exception of the midday meal when exenatide was not administered. Mechanisms controlling

postprandial glucose differ between these therapies: whereas both exenatide and rapid-acting insulin analogs suppress hepatic glucose output and stimulate peripheral glucose uptake (18,19), only short-acting GLP-1 receptor agonists decelerate gastric emptying (23,24), resulting in slower meal-derived carbohydrate entry into the circulation. The importance of decelerated gastric emptying is demonstrated by the reduction of postmeal insulin responses with exenatide (24) despite the insulinotropic potential of GLP-1 receptor

Table 2—Characteristics and results of patients at randomization and at study end point

Characteristic/variable	Exenatide (n = 247)	Lispro (n = 263)	Exenatide-lispro
Demographics			
Men	128 (52%)	133 (51%)	
Age (years), mean (SD)	59.5 (9.6)	59.4 (9.3)	
Duration of diabetes (years), median (IQR)	12 (8–17)	11 (8–15)	
Ethnic origin			
White	222 (90%)	229 (87%)	
Asian	11 (5%)	14 (5%)	
African American	2 (<1%)	1 (<1%)	
Other*	12 (5%)	18 (7%)	
Use of glucose-lowering agents			
Metformin daily dose (mg), mean (SD)	2,038 (633)	1,998 (648)	
Previous sulfonylurea use	85 (34%)	99 (38%)	
Insulin glargine (units/day)			
Randomization, mean (SD)	61.5 (30.9)	61.1 (35.2)	
End point, mean (SD)	56.9 (29.4)	51.5 (31.4)	
End point, LS mean (SE) (95% CI)†	56.8 (1.2)	51.5 (1.2)	5.3 (2.1, 8.5)‡
Randomization, median (IQR)	54 (40–76)	52 (38–76)	
End point, median (IQR)	50 (36–74)	46 (34–62)	
Insulin lispro (units/day)			
1 week, mean (SD)	—	24.6 (12.7)	
End point, mean (SD)	—	42.1 (30.8)	
1 week, median (IQR)	—	22 (16–30)	
End point, median (IQR)	—	34 (24–52)	
Insulin glargine + insulin lispro (units/day)			
1 week, mean (SD)	—	64.0 (32.9)	
End point, mean (SD)	—	93.7 (53.9)	
1 week, median (IQR)	—	56 (42–80)	
End point, median (IQR)	—	82 (60–108)	
Exenatide (μg/day)			
1 week, mean (SD)	9.9 (0.8)	—	
End point, mean (SD)	18.6 (3.6)	—	
Randomization, median (IQR)	10 (10–10)	—	
End point, median (IQR)	20 (20–20)	—	
Glycemic measures			
HbA _{1c} (%) [mmol/mol]			
Randomization, mean (SD)	8.3 (1.0) [67 (11)]	8.2 (0.9) [66 (10)]	
End point, mean (SD)	7.2 (1.0) [55 (11)]	7.2 (1.0) [55 (11)]	
Change from randomization, LS mean (SE) (95% CI)†	−1.13 (0.05) [−12.4 (0.5)]	−1.10 (0.05) [−12.0 (0.5)]	−0.04 (−0.18, 0.11)
Patients with HbA _{1c} ≤7% (% [95% CI])	49.6 [42.6, 55.4]	49.0 [42.9, 55.3]	
Patients with HbA _{1c} ≤6.5% (% [95% CI])	26.2 [20.6, 31.8]	25.5 [20.3, 31.2]	
FG (mmol/L)			
Randomization, mean (SD)	7.1 (2.3)	7.1 (2.5)	
End point, mean (SD)	6.5 (2.0)	7.2 (2.8)	
Change from randomization, LS mean (SE) (95% CI)†	−0.46 (0.16)	0.18 (0.15)	−0.64 (−1.05, −0.24)§
Self-monitored blood glucose (mmol/L)¶			
Morning 2 h postmeal			
Randomization, mean (SD)	9.97 (2.94)	10.21 (2.89)	
End point, mean (SD)	7.42 (1.97)	7.74 (2.10)	
Change from randomization, LS mean (SE) (95% CI)†	−2.57 (0.14)	−2.30 (0.14)	−0.27 (−0.63, 0.09)
Midday 2 h postmeal			
Randomization, mean (SD)	10.4 (2.7)	10.9 (3.0)	
End point, mean (SD)	8.5 (2.4)	7.6 (2.2)	
Change from randomization, LS mean (SE) (95% CI)†	−2.18 (0.16)	−3.11 (0.16)	0.93 (0.52, 1.34)
Evening 2 h postmeal			
Randomization, mean (SD)	10.9 (3.2)	11.1 (2.9)	
End point, mean (SD)	8.2 (2.6)	7.8 (2.4)	
Change from randomization, LS mean (SE) (95% CI)†	−2.88 (0.17)	−3.16 (0.17)	0.28 (−0.16, 0.72)
1,5 anhydroglucitol (μg/mL)**			
Randomization, median (IQR)	5.7 (3.2–9.0)	5.1 (2.9–9.1)	
End point, median (IQR)††	9.8 (5.3–14.0)	10.0 (5.5–15.4)	
Change from randomization, LS mean (SE) (95% CI)‡‡	1.2 (3.0)	5.3 (3.0)	−4.2 (−11.4, 3.1)

Continued on p. 2769

Table 2—Continued

Characteristic/variable	Exenatide (n = 247)	Lispro (n = 263)	Exenatide-lispro
Fasting glucagon (pmol/L)			
Randomization, mean (SD)	24.8 (10.1)	24.3 (9.2)	
End point, mean (SD)	25.6 (12.0)	24.3 (10.1)	
Change from randomization, LS mean (SE) (95% CI)††	1.3 (0.7)	0.3 (0.7)	1.1 (−0.6, 2.7)
Weight and composite measures			
BMI (kg/m ²)			
Randomization, mean (SD)	32.7 (4.7)	32.3 (4.7)	
End point, mean (SD)	31.8 (4.6)	33.1 (5.1)	
Change from randomization, LS mean (SE) (95% CI)†	−0.9 (0.1)	0.8 (0.1)	−1.7 (−1.9, −1.4)
Body weight (kg)			
Randomization, mean (SD)	91.1 (16.6)	89.4 (17.0)	
End point, mean (SD)	88.6 (16.5)	91.4 (17.9)	
Change from randomization, LS mean (SE) (95% CI)†	−2.5 (0.3)	2.1 (0.2)	−4.6 (−5.2, −3.9)
Waist circumference (cm)			
Randomization, mean (SD)	108 (13)	108 (13)	
End point, mean (SD)	106 (13)	108 (14)	
Change from randomization, LS mean (SE) (95% CI)†	−2.0 (0.4)	0.7 (0.3)	−2.7 (−3.6, −1.8)
Hip circumference (cm)			
Randomization, mean (SD)	110 (12)	110 (11)	
End point, mean (SD)	109 (11)	111 (12)	
Change from randomization, LS mean (SE) (95% CI)†	−1.8 (0.4)	0.9 (0.4)	−3.0 (−3.6, −1.9)
HbA _{1c} ≤7% and ≤1 kg weight gain (% [95% CI])	44.6 [37.4, 50.2]	22.9 [17.9, 28.4]	
HbA _{1c} ≤6.5% and ≤1 kg weight gain (% [95% CI])	23.1 [17.6, 28.4]	14.5 [10.4, 19.3]§§	
Cardiovascular parameters			
Systolic blood pressure (mmHg)			
Randomization, mean (SD)	137 (16)	135 (15)	
End point, mean (SD)	133 (14)	136 (16)	
Change from randomization, LS mean (SE) (95% CI)†	−4.1 (1.0)	0.4 (0.9)	−4.5 (−7.0, −2.0)
Diastolic blood pressure (mmHg)			
Randomization, mean (SD)	79 (10)	78 (9)	
End point, mean (SD)	79 (10)	79 (10)	
Change from randomization, LS mean (SE) (95% CI)†	−0.6 (0.6)	−0.1 (0.6)	−0.5 (−2.1, 1.1)
Pulse rate (beats per min)			
Randomization, mean (SD)	74 (11)	73 (10)	
End point, mean (SD)	75 (11)	74 (11)	
Change from randomization, LS mean (SE) (95% CI)†	1.5 (0.6)	0.9 (0.6)	0.6 (−1.1, 2.2)
Cholesterol (mmol/L)			
Total cholesterol			
Randomization, mean (SD)	4.6 (1.0)	4.6 (1.0)	
End point, mean (SD)	4.5 (1.0)	4.6 (1.1)	
Change from randomization, LS mean (SE) (95% CI)††	−0.1 (0.1)	−0.0 (0.0)	−0.1 (−0.2, 0.0)
LDL cholesterol			
Randomization, mean (SD)	2.5 (0.8)	2.6 (0.9)	
End point, mean (SD)	2.5 (0.8)	2.6 (0.9)	
Change from randomization, LS mean (SE) (95% CI)††	−0.1 (0.0)	−0.0 (0.0)	−0.1 (−0.2, 0.0)
HDL cholesterol			
Randomization, mean (SD)	1.2 (0.3)	1.2 (0.3)	
End point, mean (SD)	1.2 (0.3)	1.2 (0.3)	
Change from randomization, LS mean (SE) (95% CI)††	−0.04 (0.01)	0.03 (0.01)	−0.07 (−0.10, −0.04)
Triglycerides (mmol/L)			
Randomization, median (IQR)	1.6 (1.2–2.1)	1.5 (1.1–2.0)	
End point, median (IQR)	1.6 (1.2–2.3)	1.4 (1.1–2.0)	
Change from randomization, LS mean (SE) (95% CI)††	0.06 (0.06)	−0.05 (0.06)	0.11 (−0.03, 0.24)
Adiponectin (ng/L)**			
Randomization, median (IQR)	5,771 (3,957–7,737)	5,406 (3,869–7,778)	
End point, median (IQR)	6,061 (4,103–8,581)	5,201 (3,541–7,985)	
Change from randomization, LS mean (SE) (95% CI)††	−491 (247)	−651 (249)	160 (−430, 750)
hs-CRP (mg/L)**			
Randomization, mean (SD)	4.9 (5.7)	4.5 (5.9)	
End point, mean (SD)††	4.3 (6.6)	4.9 (6.5)	
Change from randomization, LS mean (SE) (95% CI)††	−0.6 (0.4)	0.2 (0.4)	−0.8 (−1.7, 0.1)
Randomization, median (IQR)	3.2 (1.5–6.2)	2.6 (1.3–5.4)	
End point, median (IQR)	2.7 (1.1–5.3)	2.7 (1.1–5.9)	

Continued on p. 2770

Table 2—Continued

Characteristic/variable	Exenatide (n = 247)	Lispro (n = 263)	Exenatide-lispro
Urine albumin/creatinine (mg/mmol)**			
Randomization, median (IQR)	1.6 (0.6–5.0)	1.4 (0.6–5.2)	
End point, median (IQR)††	1.1 (0.5–2.9)	1.2 (0.5–5.2)	
Change from randomization, LS mean (SE) (95% CI)‡‡	–4.2 (2.6)	–3.7 (2.6)	–0.5 (–6.7, 5.7)

All values are for the PP population unless otherwise noted. LS, least squares. *American Indian or Native Alaskan. †Calculated using MMRM. ‡P = 0.001. §P = 0.002. ¶From self-monitored blood glucose profiles. ||P < 0.001. **ITT population. ††End point values are last observation carried forward. ‡‡Calculated using ANCOVA at end point for change from randomization. §§P = 0.005.

stimulation (23). It is unknown whether similar efficacy can be obtained by combining long-acting GLP-1 receptor agonists with basal insulin because long-acting formulations have less impact on gastric emptying delay and thus reduce mealtime glucose less than short-acting formulations (25). Different mechanisms of action may explain differential risk of nonnocturnal hypoglycemic events, which largely occurred postmeal. The use of rapid-acting insulin analogs is associated with increased hypoglycemia risk (26,27), whereas GLP-1 receptor agonists are associated with low risk of hypoglycemia due to glucose-dependent action (4). Most hypoglycemic events were reported after 12 weeks postrandomization (Supplementary Fig. 3B), when HbA_{1c} and glargine doses were stable, suggesting that hypoglycemia was associated with lispro. The similar incidence of nocturnal hypoglycemia was likely attributable to glargine, as both lispro and exenatide, having short half-lives, were administered during the day.

The observed difference in weight may be important over time as weight gain contributes to both insulin resistance and cardiovascular risk (1,28). Combined improvements in HbA_{1c}, weight, and blood pressure may also favorably affect cardiovascular risk. Although HDL cholesterol was lowered with exenatide, total cholesterol and LDL cholesterol were also lowered by both treatments (the between-group difference did not reach statistical significance).

Patient adherence is an important factor in any therapeutic regimen and is associated with clinical and economic benefits (29). It is possible that some of the randomized patients failed basal insulin during BIO-phase due to unwillingness to titrate, so clinical data on patient adherence to these regimens are needed.

A patient's perception of how treatment affects his or her life is an important clinical consideration and may affect adherence (1). Improved treatment satisfaction was previously noted with GLP-1 receptor agonists (22,30). Here, increased treatment satisfaction was observed for both regimens, suggesting that patients value clinical improvements more than they oppose injections (22,30). Factors such as weight loss, less hypoglycemia, or some combination thereof, may provide greater improvement in treatment satisfaction with exenatide, despite more gastrointestinal adverse effects.

The insulin titration protocols chosen for this study may be considered a study limitation. In general, patient care and follow-up procedures were intended to reflect daily clinical practice, allow individualization of patient care according to clinical judgment, and minimize hypoglycemia risk. Dosing instructions were more straightforward for the exenatide group, for whom routine glargine titration was not reduced at randomization except for patients with an HbA_{1c} of 8.0% or less at introduction of exenatide. To support patient safety, glargine in these patients was reduced by 10% since a previous study of this combination demonstrated acceptable hypoglycemia rates with a 20% initial reduction of glargine in patients with HbA_{1c} of 8.0% or less (3). In contrast, the titration protocols for glargine with lispro were based on or similar to ongoing or recently completed trials of basal-bolus insulin (the IOOQ Study [7] and IOOV/DURABLE Study [8]). The division of daily insulin dose into 50% basal and 50% bolus insulin was common practice when this study was initiated (31), and the final total daily insulin dose was consistent with published studies (32). Nevertheless, some physicians now initiate bolus insulin with the more recent "basal-plus" method in which basal

insulin is not reduced and low doses of bolus insulin are added to one or more meals a day (32). The results of comparing a "basal-plus" strategy with addition of exenatide to basal insulin are not known, but we believe the approach used for initiating insulin will not affect the overall results of the study, particularly differences in body weight and hypoglycemia incidence. Addition of exenatide to glargine was associated with improvement in multiple clinical and patient-reported outcome measures, and this approach was supported as viable for routine clinical practice. It remains possible that more efficacious insulin treatment regimens will be developed in the future, for instance those using the new long-acting analogs.

Discontinuation rates, while significant, were consistent with similar studies (3,13). In the exenatide arm, one patient was diagnosed with pancreatic cancer after treatment with exenatide for 71 days. The patient discontinued exenatide and the study and died 1.5 years poststudy. No other cancers were observed in either arm. Based on the time course, it is unlikely that there is a causal relationship with the use of exenatide. Type 2 diabetes itself has been associated with an increased risk of various types of cancer, including pancreatic cancer (33). In a recent review, Nauck and Friedrich (34) reported that there is no firm evidence that supports the hypothesis that GLP-1–based therapy can increase the risk for specific malignant diseases like pancreatic carcinoma and thyroid cancer, nor is there firm evidence to rule out any such increased risk based on results available at present. These conclusions have recently been affirmed by the U.S. Food and Drug Administration and the European Medicines Agency (35).

Other limitations of our study include no extensive mechanistic measurements

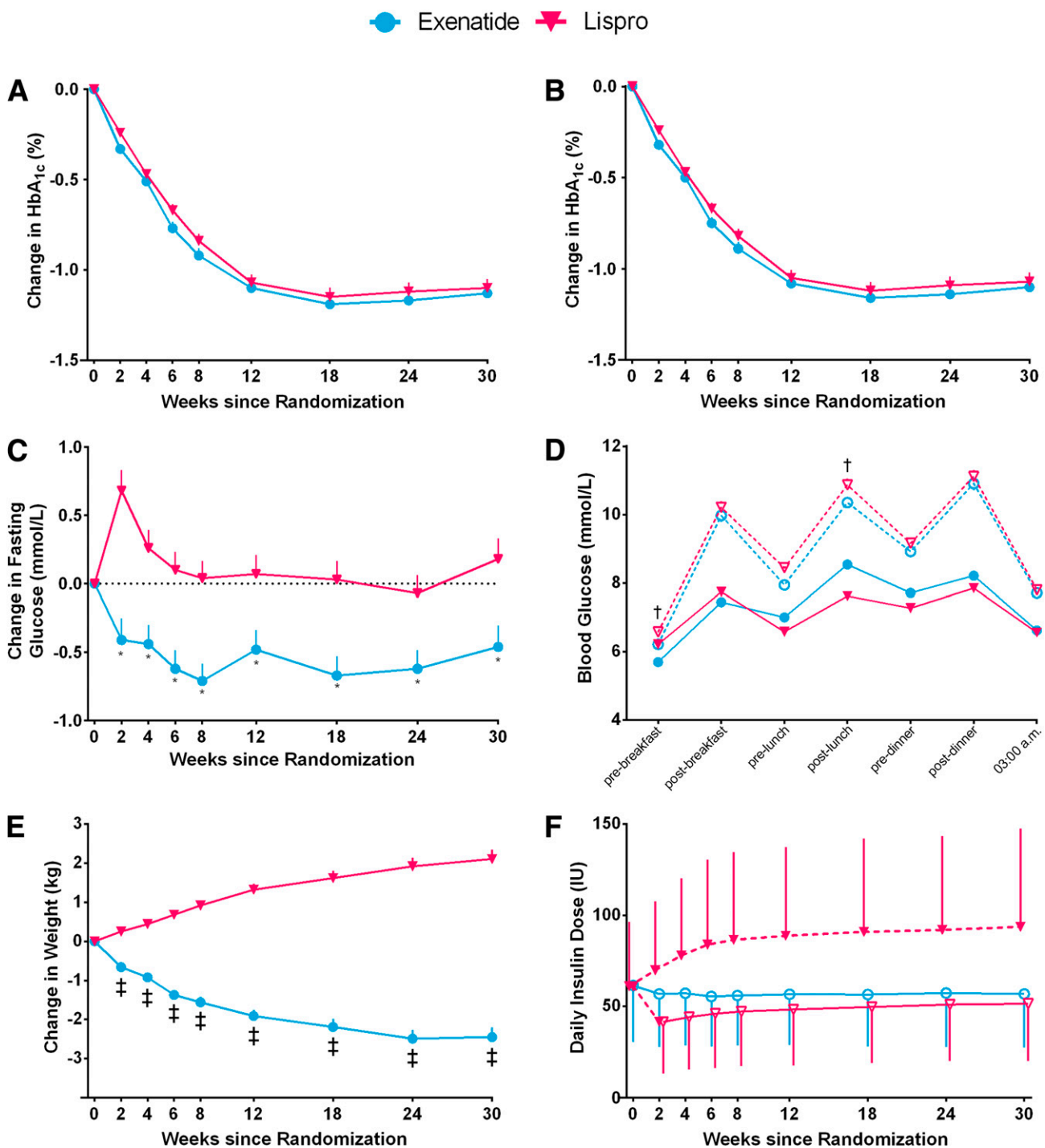


Figure 2—Primary and secondary outcomes from randomization to 30 weeks. *A*: Least-squares (LS) mean change (SE) in HbA_{1c} values from the MMRM model in the PP population. *B*: LS mean change (SE) in HbA_{1c} values from the MMRM model in the ITT population. *C*: LS mean change (SE) for FG in the PP population (**P* = 0.002). *D*: Self-monitored blood glucose mean values (SE) at randomization (open symbols, dashed lines) and at 30 weeks (closed symbols, solid line) (†*P* < 0.001, lispro vs. exenatide). *E*: LS mean change (SE) for weight in the PP population (‡*P* < 0.001). *F*: Insulin dose (units/day) mean (SD) for basal insulin glargine in the exenatide and lispro arms (open symbols) and the total insulin dose (glargine plus lispro) in the lispro arm (closed symbol).

and past use of diverse therapies. Furthermore, guidance for treating patients who fail despite exenatide addition, which may include rapid-acting insulin, is absent. Lastly, while these data demonstrate the safety and tolerability of

exenatide compared with lispro when added to glargine over 30 weeks, additional studies are needed to provide data on the long-term use of these therapies.

Insulin and its analogs have long been the only injectable option for patients

with advanced type 2 diabetes. Exenatide, like insulin, also requires injection, albeit with fixed dosing, fewer daily injections, and less need for glucose monitoring. The findings of similar HbA_{1c} reduction but less nocturnal hypoglycemia, more

weight loss, and improved treatment satisfaction for addition of exenatide instead of lispro to titrated basal insulin challenge current treatment recommendations (1) by suggesting that adding a short-acting GLP-1 receptor agonist to basal insulin may be preferred over mealtime and basal insulin for some patients with type 2 diabetes.

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The sponsor took part in study design, safety monitoring, data collection, data analysis, data interpretation, and writing of the report.

Author Contributions. M.D. and B.H.R.W. were principal investigators of the study and contributed to the design and conduct of the study, researching data, interpreting and discussing results, writing the manuscript, and critically revising all subsequent versions. M.A.N. contributed to researching data, interpreting and discussing results, drafting parts of the manuscript, and revising all subsequent versions. R.S. was the lead physician of the study, wrote the protocol, and contributed to the design and conduct of the study, researching data, interpreting and discussing results, writing the manuscript, and revising all subsequent versions. J.K.M., B.J.H., and L.M. contributed to the design and conduct of the study, researching data, interpreting and discussing results, writing the manuscript, and revising all subsequent versions. S.C. was involved in the study design, conduct, data analysis, data interpretation, manuscript writing, and revising all subsequent versions. M.R. was involved in the study design, conduct, data interpretation, manuscript writing, and revising all subsequent versions. D.d.V. was clinical trial manager for the study and was involved in the study design, conduct, data interpretation, results discussions and manuscript writing, and revising all subsequent versions. B.H.R.W. agreed to submit the final version of the manuscript for publication. All authors had full access to the data and responsibility for the content of the report. All authors had final responsibility for the decision to submit. B.H.R.W. 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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