Prandial Options to Advance Basal Insulin Glargine Therapy: Testing Lixisenatide Plus Basal Insulin Versus Insulin Glulisine Either as Basal-Plus or Basal-Bolus in Type 2 Diabetes: The GetGoal Duo-2 Trial

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OBJECTIVE

To provide evidence-based options on how to intensify basal insulin, we explored head-to-head prandial interventions in overweight patients with type 2 diabetes inadequately controlled on basal insulin glargine with or without 1–3 oral antidiabetic agents (OADs).

RESEARCH DESIGN AND METHODS

Patients were randomized to lixisenatide once daily or insulin glulisine given once or thrice daily, added to glargine, with or without metformin, if HbA_{1c} remained ≥7 to ≤9% (≥53 to ≤75 mmol/mol) after 12 weeks of glargine optimization with OADs other than metformin stopped at the start of optimization. Coprimary end points at 26 weeks were *1*) noninferiority (95% CI upper bound <0.4% [<4.4 mmol/mol]) in HbA_{1c} reduction with lixisenatide versus glulisine once daily, and either *2a*) noninferiority in HbA_{1c} reduction for lixisenatide versus glulisine thrice daily or *2b*) superiority in body weight change for lixisenatide versus glulisine thrice daily. Fasting and postprandial plasma glucose, composite efficacy/safety end points, and adverse events were also assessed.

RESULTS

Baseline characteristics were similar between arms (*n* = 298, diabetes and basal insulin duration of 12.2 and 3.2 years, respectively; BMI 32.2 kg/m^2). HbA_{1c} improved from 8.5% to 7.9% (69 to 63 mmol/mol) with glargine optimization and further to 7.2%, 7.2%, and 7.0% (55, 55, and 53 mmol/mol) with lixisenatide and glulisine once daily and thrice daily, respectively; all coprimary end points were met. Symptomatic hypoglycemia and body weight were lower in lixisenatide versus glulisine patients. More gastrointestinal events occurred with lixisenatide.

CONCLUSIONS

Short-acting glucagon-like peptide-1 receptor agonists as add-on to basal insulin may become a preferred treatment intensification option, attaining meaningful glycemic targets with fewer hypoglycemic events without weight gain versus basal-plus or basal-bolus in uncontrolled basal insulin-treated type 2 diabetes.

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The conventional recommendation in type 2 diabetes inadequately controlled with basal insulin plus oral antidiabetic agents (OADs) has been the addition of a prandial insulin as a single injection with the main meal (basal-plus) or progressively covering all meals (basal-bolus) (1).

Evidence from a randomized head-to-head trial comparing initiation of insulin glargine plus insulin glulisine as basal-plus or basal-bolus versus twice-daily premixed insulin demonstrated that these regimens can achieve substantial and comparable reductions in HbA_{1c} to almost 7% (53 mmol/mol) over 60 weeks (2). However, hypoglycemia and weight gain occurred in each prandial insulin injection group. Indeed, unacceptable weight gain and hypoglycemia are pressing issues in the management of type 2 diabetes, and hypoglycemic risk increases as type 2 diabetes advances, impeding attainment of glycemic targets (3).

The recently updated American Diabetes Association/European Association for the Study of Diabetes treatment guidelines have largely reiterated this prandial insulin recommendation but also proposed the option of adding a glucagon-like peptide-1 receptor agonist (GLP-1 RA) to basal insulin (4). Although these updated guidelines emphasize the importance of individualizing treatment and go some way toward revising the existing treatment paradigm, they are not evidence-based, because the three injectable options (GLP-1 RA, basal insulin, and prandial insulin) have not been compared directly in a single properly controlled study to address the multiple issues affecting outcomes (5).

GLP-1 RAs improve glycemia without substantially increasing hypoglycemic risk and without weight gain. Lixisenatide (Lyxumia; Sanofi, Paris, France) is a once-daily prandial GLP-1 RA with robust postprandial glucose (PPG)-lowering effect, predominantly via delayed gastric emptying and glucose-dependent reductions in glucagon release (6–9).

The GetGoal Duo-1 trial was the first study to assess the efficacy of lixisenatide in combination with optimally titrated basal insulin in patients with type 2 diabetes uncontrolled on OADs who were newly initiating insulin glargine. Significant reductions in HbA_{1c} to 7% (53 mmol/mol) and marked PPG reductions were achieved with the addition of lixisenatide plus basal insulin versus basal insulin alone (10).

The present 26-week trial (GetGoal Duo-2) took the above findings further and evaluated head-to-head in a randomized fashion the efficacy and safety of lixisenatide 20 μg once daily versus insulin glulisine once daily (basal-plus) or thrice daily (basal-bolus) for intensification of optimized insulin glargine, with or without metformin, in uncontrolled patients on basal insulin with or without OADs. It is hoped that this trial will provide evidence-based data to aid in the clinical decision-making process for individualization of basal insulin-based therapy in patients with type 2 diabetes when intensification of treatment is required.

RESEARCH DESIGN AND METHODS

Trial Design

GetGoal Duo-2 was a randomized, open-label, active comparator trial with three parallel arms conducted at 199 centers in 18 countries. The study was initiated in January 2013 and completed in December 2014. Adults with type 2 diabetes uncontrolled on ≥6 months' basal insulin, with or without 1–3 OADs, were eligible to enter a 12-week run-in period. On run-in entry, OADs other than metformin (dipeptidyl peptidase-4 [DPP-4] inhibitors, sulfonylureas [SU], and glinides) were discontinued, and insulin glargine was optimally titrated. After the run-in phase, if HbA_{1c} remained between ≥7 and ≤9% (≥53 and ≤75 mmol/mol) and mean fasting plasma glucose (FPG) was ≤140 mg/dL (≤7.8 mmol/L), patients were randomized 1:1:1 (by interactive voice or Web response system), and stratified by baseline HbA_{1c} (<8 or ≥8% [<64 or >64 mmol/mol]) and metformin use, to receive subcutaneous lixisenatide once daily or insulin glulisine once or thrice daily as add-on therapy to insulin glargine with or without metformin. The trial comprised three periods (Supplementary Fig. 1): *1*) a screening phase of up to 2 weeks, followed by a 12-week run-in phase; *2*) 26 weeks of open-label, randomized treatment; and *3*) 3 days of follow-up. 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 at each center.

Study Population

Adults with type 2 diabetes for at least 1 year and a BMI >20.0–40.0 kg/m^2 were eligible for screening. Patients were on basal insulin for at least 6 months at screening (stable dose ≥20 units/day for ≥2 months before screening), alone or combined with stable doses of 1–3 OADs (metformin [≥1.5 mg/day or maximum tolerated dose], a DPP-4 inhibitor, an SU, or a glinide). Patients receiving basal insulin alone or with metformin had to have HbA_{1c} 7.5–10.0% (58–86 mmol/mol) at screening. Patients receiving basal insulin plus an SU and/or a DPP-4 inhibitor and/or a glinide had to have HbA_{1c} 7.0–10.0% (53–86 mmol/mol) at screening. Because all OADs other than metformin were discontinued at the start of the run-in phase, the two different HbA_{1c} thresholds were necessary to compensate for the subsequent expected increase in HbA_{1c} in the latter group.

Exclusion criteria included a clinically relevant history of gastrointestinal disease or a history of unexplained/chronic pancreatitis. Patients were excluded if they had alanine/aspartate aminotransferase, amylase, or lipase levels more than three times the upper limit of normal or calcitonin levels >20 pg/mL.

Run-in Phase

During run-in, insulin glargine was introduced (for patients previously on a different basal insulin) or continued as part of a once-daily regimen, at breakfast or at the evening meal, as determined at the start of the run-in period, and titrated every 3 days to achieve fasting self-monitored plasma glucose (SMPG) between 80 and 100 mg/dL (4.4 and 5.6 mmol/L) while avoiding hypoglycemia (11).

Randomized Treatment Phase

Insulin glargine doses were adjusted weekly to maintain fasting daily SMPG between 80 and 100 mg/dL (4.4 and 5.6 mmol/L) except during the 4 weeks after randomization when a stable insulin dose was maintained. Timing of insulin glargine injections was established during the run-in, whereas timing of the once-daily prandial intervention was based on the main meal during the week before randomization. Patients randomized to receive lixisenatide were administered 10 μg once daily for 2 weeks, followed by lixisenatide 20 μg once daily for the remainder of the study, injected 30–60 min before the main meal, as defined above. Further details on study

medication administration can be found in the Supplementary Appendix.

Assessments

Coprimary objectives at week 26 were: *1*) noninferiority of lixisenatide versus insulin glulisine once daily in HbA_{1c} reduction; and for lixisenatide versus insulin glulisine thrice daily, either *2a*) noninferiority in HbA_{1c} reduction or *2b*) superiority of lixisenatide versus insulin glulisine thrice daily in body weight change.

Secondary objectives assessed at week 26 included change from baseline in FPG, change from baseline in PPG during standardized meal tests in patients who received an injection of study medication before breakfast (meal test using Ensure Plus [Abbott Laboratories]; 600 kcal, carbohydrate 50–55%, protein 15–20%, and fat 25–30%), percentage of patients who achieved HbA_{1c} <7 or ≤6.5% (<53 or ≤48 mmol/mol), change from baseline in body weight, 7-point SMPG profile, and daily insulin dose. Composite end points assessed at week 26 were the percentage of patients achieving HbA_{1c} <7% (<53 mmol/mol) with no weight gain; HbA_{1c} <7% (<53 mmol/mol) without documented symptomatic hypoglycemia (glucose <60 mg/dL [<3.3 mmol/L]; and HbA_{1c} <7% [<53 mmol/mol]), no weight gain, and no documented symptomatic hypoglycemia.

Adverse events (AEs), serious AEs, vital signs, and laboratory values, including amylase and lipase, were monitored throughout the trial. Symptomatic hypoglycemia AEs included any event accompanied by typical signs and/or symptoms of hypoglycemia reported by the study investigator, and as defined per protocol, included symptomatic events accompanied by glucose <60 mg/dL (<3.3 mmol/L) or, if no glucose measurement was available, associated with prompt recovery with oral carbohydrate. Severe hypoglycemia was defined as the patient requiring assistance along with a glucose measurement 36 mg/dL (<2.0 mmol/L) or, if no glucose measurement was available, prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration.

Statistical Methods

Assuming a dropout rate of 20%, a common standard deviation of 1.2%, and a true difference in HbA_{1c} between the treatment groups of zero, it was determined that a sample size of 285 patients per treatment arm (855 patients in total) would ensure that the upper limit of the two-sided 95% CI for the adjusted mean difference in change from baseline at week 26 in HbA_{1c} between the lixisenatide and the insulin glulisine once-daily arms would not exceed 0.4% (4.4 mmol/mol) with at least 94% power. This sample size also ensured that the upper limit of the two-sided 97.5% CI for the adjusted mean difference in change from baseline at week 26 in HbA_{1c} between the lixisenatide and the insulin glulisine thrice-daily arms would not exceed 0.4% (4.4 mmol/mol) with at least 90% power; and at least 90% power to detect a difference of 1 kg in change from baseline in body weight at week 26 between the lixisenatide and the insulin glulisine thrice-daily arms, assuming a common SD of 2.75 kg at the 2.5% significance level (two-sided).

The modified intent-to-treat population (all randomized patients with at least one dose of study medication and a baseline assessment and at least one assessment after baseline of any primary or secondary efficacy end point) was used for all efficacy analyses, other than assessment of PPG (assessed in patients who received an injection of study medication before breakfast). The safety analysis was conducted on the safety population (all randomized patients who received at least one dose of study medication regardless of the amount of treatment administered).

Overall, statistical analyses were assessed at a significance level of 0.025 (one-sided). End points 1 and 2 (2a or 2b) were assessed separately at a significance level of 0.025 (one-sided). For coprimary end point 1, lixisenatide was declared noninferior to insulin glulisine once daily if the upper bound of the two-sided 95% CI for treatment difference was <0.4% (<4.4 mmol/mol) as determined based on regulatory recommendations at the time of the protocol preparation and on other studies with similar compounds (12,13). For coprimary end points 2a and 2b, a Hochberg procedure was used to control for type I error as follows: if both end points 2a and 2b were met at α = 0.025 (one-sided), then the entire end point 2 was met at α = 0.025 (one-sided); if only end point 2a or 2b was achieved at α = 0.025 (one-sided), then the end point that was met was tested at α = 0.0125 (one-sided). If coprimary end points 1 and 2 were both met at α = 0.025 (one-sided), the study was considered positive.

Coprimary end points were analyzed using an ANCOVA model with treatment, week − 1 strata of HbA_{1c} (<8 or ≥8% [<64 or ≥64 mmol/mol]), randomization strata of metformin use (yes or no), and country as fixed effects, and using the corresponding baseline value as a covariate. Missing data in the analysis of the coprimary end points were imputed using the last observation carried forward method.

All continuous secondary efficacy end points, except insulin glulisine and total daily insulin dose, were analyzed using the same primary ANCOVA model as described above. All categorical secondary efficacy end points were analyzed using a Cochran–Mantel–Haenszel method stratified on week − 1 HbA_{1c} (<8 or ≥8% [<64 or ≥64 mmol/mol]) and randomization strata of metformin use (yes or no). Multiplicity adjustments were not performed for secondary efficacy end points.

In the efficacy analysis, patients were analyzed in the treatment group to which they were randomized, irrespective of compliance with the study protocol.

RESULTS

Between 8 January 2013 and 3 December 2014, 2,159 patients were screened and 894 patients were randomized (Supplementary Fig. 2). The most frequent reason for run-in failure was that HbA_{1c} criteria were not met at the end of the run-in period. Treatment discontinuations occurred in 30 (10.1%), 17 (5.7%), and 12 (4.0%) of the 298 patients in the lixisenatide and insulin glulisine once-daily and thrice-daily arms, respectively (Supplementary Fig. 2). Insulin glargine was administered by 26% of patients in the morning and by 74% in the evening. Both lixisenatide and insulin glulisine once daily were administered by 30% of patients at breakfast and by 70% at the evening meal.

Baseline characteristics were similar across treatment groups (Table 1). Approximately 90% of patients were receiving (and continued) treatment with metformin. At screening, the overall mean durations of type 2 diabetes and basal insulin treatment were 12.2 and 3.2 years, respectively. Mean overall body weight was 89.1 kg and mean BMI was 32.2 kg/m^2. At screening, mean ± SD HbA_{1c} for the total randomized

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

Parameters	Insulin glargine with or without metformin plus		
	Lixisenatide 20 μg once daily (*n* = 298)	Insulin glulisine once daily (*n* = 298)	Insulin glulisine thrice daily (*n* = 298)
Age at screening, years	59.8 ± 8.6	60.2 ± 8.6	59.4 ± 9.5
Male, *n* (%)	138 (46.3)	135 (45.3)	132 (44.3)
White, *n* (%)	276 (92.6)	280 (94.0)	272 (91.3)
BMI, kg/m^2	32.3 ± 4.6	31.9 ± 4.4	32.5 ± 4.6
Body weight, kg			
Start of run-in	89.8 ± 17.4	87.9 ± 15.8	89.7 ± 17.3
End of run-in	90.2 ± 17.5	88.4 ± 15.8	90.1 ± 17.3
HbA_{1c}, % (mmol/mol)			
Screening	8.5 ± 0.7 (69 ± 7.7)	8.5 ± 0.7 (69 ± 7.7)	8.5 ± 0.8 (69 ± 8.7)
End of run-in	7.9 ± 0.5 (63 ± 5.5)	7.8 ± 0.5 (62 ± 5.5)	7.9 ± 0.5 (63 ± 5.5)
FPG, mmol/L (mg/dL)			
Start of run-in	9.2 ± 2.9 (165 ± 53)	9.3 ± 2.9 (167 ± 52)	9.5 ± 3.0 (171 ± 53)
End of run-in	6.9 ± 2.1 (125 ± 37)	6.8 ± 1.8 (122 ± 32)	6.7 ± 1.9 (119 ± 34)
Variables at screening			
Duration of type 2 diabetes, years	11.9 ± 6.4	12.3 ± 6.8	12.4 ± 6.8
Duration of basal insulin treatment, years	3.1 ± 2.6	3.3 ± 3.5	3.2 ± 3.1
Daily basal insulin dose, units/day			
NPH insulin	41 ± 20	39 ± 18	41 ± 20
Insulin glargine	42 ± 23	41 ± 23	40 ± 23
Insulin detemir	41 ± 30	40 ± 25	39 ± 22
OAD use, *n* (%)			
Metformin	262 (87.9)	260 (87.2)	259 (86.9)
SU	141 (47.3)	129 (43.3)	142 (47.7)
DPP-4 inhibitor	37 (12.4)	29 (9.7)	42 (14.1)
Insulin glargine dose, units/day			
Start of run-in	41 ± 22	40 ± 22	39 ± 21
End of run-in	68 ± 32	65 ± 32	65 ± 27
Patients with evening insulin glargine dosing,* %	73.5	76.8	73.0
Patients with study drug administration at:			
Breakfast, %	30.2	29.5	–
Evening meal, %	69.5	69.8	–
Missing, %	0.3	0.7	–

Data are presented as the mean ± SD or as indicated. All data are for screening except where indicated otherwise. Start of run-in, week – 12; end of run-in, week – 1. *Data available for 283 lixisenatide-treated patients and 289 patients in each insulin glulisine arm; evening dosing defined as any dose administered between 1600 and 0400 h.

study population was 8.5 ± 0.7% (69 ± 7.7 mmol/mol), and at the start of run-in, mean ± SD FPG was 168 ± 53 mg/dL (9.3 ± 2.9 mmol/L). Overall mean ± SD HbA_{1c} and FPG at the end of the week-12 glargine optimization period decreased to 7.9 ± 0.5% (63 ± 5.5 mmol/mol) and 122 ± 34 mg/dL (6.8 ± 1.9 mmol/L), respectively. During the optimization period, the overall insulin glargine dose increased from 40 to 66 units/day.

Coprimary End Points

All coprimary end points were met. Mean ± SD HbA_{1c} with lixisenatide declined from 7.8 ± 0.6% (62 ± 6.6 mmol/mol) at baseline to 7.2 ± 0.8% (55 ± 8.7 mmol/mol) at week 26. Mean ± SD baseline HbA_{1c} in the insulin glulisine once- and thrice-daily arms was 7.7 ± 0.6% (61 ± 6.6 mmol/mol) and 7.8 ± 0.6% (62 ± 6.6 mmol/mol) and was reduced to 7.2 ± 0.8% (55 ± 8.7 mmol/mol) and 7.0 ± 0.7% (53 ± 7.7 mmol/mol), respectively, at week 26 (Table 2). The least squares (LS) mean treatment difference (95% CI) for change in HbA_{1c} from baseline to end of study for lixisenatide versus insulin glulisine once daily was –0.1% (–0.17, 0.06) (–0.5 mmol/mol [–1.9, 0.7]) and versus insulin glulisine thrice daily was 0.2% (0.10, 0.33) (2.3 mmol/mol [1.0, 3.5]), meeting the predefined noninferiority criteria (upper bound of the two-sided 95% CI for treatment difference <0.4%).

At week 26, the LS mean ± SE change from baseline in body weight in the three treatment groups was –0.6 ± 0.3, +1.0 ± 0.3, and +1.4 ± 0.3 kg, for lixisenatide and insulin glulisine once daily and thrice daily, respectively (Table 2). Lixisenatide demonstrated statistical superiority in change from baseline at week 26 in body weight compared with insulin glulisine thrice daily (coprimary end point LS mean treatment difference –2.0 kg [95% CI –2.59, –1.40]; $P < 0.0001$).

Secondary End Points

Owing to optimization of insulin glargine during the run-in period, the change from baseline in FPG over 26 weeks was minimal across the three treatment arms, as was the change in the daily insulin glargine dose (Table 2). LS mean ± SE reductions from baseline in 2-h PPG after a standardized breakfast at week 26 were markedly greater in the lixisenatide arm compared with the insulin glulisine

Table 2—Response to therapy: modified intent-to-treat population

Parameters	Insulin glargine with or without metformin plus: Lixisenatide 20 μg once daily (*n* = 297)	Insulin glulisine once daily (*n* = 298)	Insulin glulisine thrice daily (*n* = 295)
FPG, mmol/L (mg/dL); *n*			
Baseline, mean ± SD	6.6 ± 1.8 (119 ± 33); 295	6.9 ± 2.0 (123 ± 36); 295	6.7 ± 1.9 (120 ± 34); 294
Week 26 LOCF, mean ± SD	6.6 ± 2.0 (119 ± 35); 295	6.7 ± 1.9 (120 ± 35); 295	6.7 ± 2.0 (121 ± 36); 294
LS mean change ± SE	−0.2 ± 0.1 (–4 ± 3); 295	−0.2 ± 0.1 (–4 ± 3); 295	−0.1 ± 0.1 (–1 ± 3); 294
LS mean (95% CI) treatment difference	–	−0.0 (–0.32, 0.30) (–0.2 [–5.7, 5.4])	−0.2 (–0.48, 0.14) (–3.0 [–8.6, 2.6])
2-h PPG, mmol/L (mg/dL);* *n/N*			
Baseline, mean ± SD	14.1 ± 3.6 (254 ± 65); 69/90	13.8 ± 3.5 (249 ± 63); 55/88	14.6 ± 3.5 (262 ± 63); 68/295
Week 26 LOCF, mean ± SD	10.2 ± 3.9 (184 ± 70); 69/90	12.2 ± 3.4 (220 ± 60); 55/88	12.7 ± 3.9 (229 ± 69); 68/295
LS mean change ± SE	−3.6 ± 0.6 (–66 ± 11); 69/90	−1.6 ± 0.6 (–28 ± 11); 55/88	−1.4 ± 0.6 (–25 ± 11); 68/295
LS mean (95% CI) treatment difference	–	−2.1 (–3.3, –0.8) (–37.3 [–59.2, –15.3])	−2.2 (–3.4, –1.1) (–40.2 [–61.1, –19.2])
HbA_{1c}, % (mmol/mol); *n*			
Baseline after 12-week run-in optimization, mean ± SD	7.8 ± 0.6 (62 ± 6.6); 292	7.7 ± 0.6 (61 ± 6.6); 292	7.8 ± 0.6 (62 ± 6.6); 295
Week 26 LOCF, mean ± SD	7.2 ± 0.8 (55 ± 8.7); 292	7.2 ± 0.8 (55 ± 8.7); 292	7.0 ± 0.7 (53 ± 7.7); 295
LS mean change ± SE	−0.6 ± 0.1 (–6.6 ± 1.1); 292	−0.6 ± 0.1 (–6.6 ± 1.1); 292	−0.8 ± 0.1 (–8.7 ± 1.1); 295
LS mean (95% CI) treatment difference	–	−0.1 (–0.17, 0.06) (–0.5 [–1.9, 0.7])	0.2 (0.10, 0.33) (2.3 [1.0, 3.5])
HbA_{1c} <7% at week 26†			
n/N (%)	123/292 (42.1)	112/292 (38.4)	145/295 (49.2)
Treatment difference, % (95% CI)	–	3.7 (–4.03, 11.49)	−7.3 (–15.07, 0.56)
HbA_{1c} ≤6.5% at week 26†			
n/N (%)	60/292 (20.5)	52/292 (17.8)	91/295 (30.8)
Treatment difference, % (95% CI)	–	2.7 (–3.59, 9.01)	−10.5 (–17.33, –3.59)
Body weight, kg; *n*			
Baseline, mean ± SD	90.1 ± 17.4; 295	88.4 ± 15.9; 295	90.0 ± 17.2; 295
Week 26 LOCF, mean ± SD	89.4 ± 18.1; 295	89.3 ± 16.3; 295	91.3 ± 17.3; 295
LS mean change ± SE	−0.6 ± 0.3; 295	1.0 ± 0.3; 295	1.4 ± 0.3; 295
LS mean (95% CI) treatment difference	–	−1.7 (–2.26, –1.06)	−2.0 (–2.59, –1.40)§
Patients with no weight gain;†‡ *n/N* (%)	191/295 (64.7)	108/295 (36.6)	90/295 (30.5)
Weighted average response rate (95% CI) treatment difference (%)	–	28.1 (20.5, 35.8)	34.2 (26.7, 41.7)
Insulin glargine dose, U/day; *n*			
Baseline, mean ± SD	67 ± 32; 292	65 ± 32; 294	65 ± 27; 294
Week 26 LOCF, mean ± SD	67 ± 36; 292	64 ± 36; 294	61 ± 29; 294
LS mean change ± SE from baseline to week 26	0.7 ± 1.0; 292	−0.1 ± 1.0; 294	−3.1 ± 1.0; 294
LS mean (95% CI) treatment difference	–	0.8 (–1.41, 2.92)	3.8 (1.66, 6.00)
Daily insulin glulisine dose, units; *n*			
Week 26 LOCF, mean ± SD	–	10 ± 8; 295	20 ± 13; 293
Total daily insulin dose (glargine + glulisine), units; *n*			
Week 26 LOCF, mean ± SD	67 ± 32; 292	74 ± 39; 295	81 ± 34; 294
Exploratory analyses			
Patients with ≥2% weight loss;† *n* (%)	97 (32.9)	33 (11.2)	32 (10.8)
Weighted average response rate treatment difference, % (95% CI)	–	21.7 (15.27, 28.11)	22.0 (15.61, 28.43)
Patients with ≥3% weight loss;† *n* (%)	69 (23.4)	21 (7.1)	18 (6.1)
Weighted average response rate treatment difference, % (95% CI)	–	16.3 (10.69, 21.97)	17.3 (11.75, 22.85)
Patients with ≥5% weight loss;† *n* (%)	36 (12.2)	11 (3.7)	7 (2.4)
Weighted average response rate treatment difference, % (95% CI)	–	8.5 (4.13, 12.86)	9.8 (5.69, 13.98)

Summary statistics (mean ± SD) for HbA_{1c}, FPG, 2-h PPG, and body weight were based on modified intent-to-treat population; all available data were included in the analysis. An ANCOVA model was used for calculation of LS mean treatment difference for HbA_{1c}, FPG, 2-h PPG, and body weight, with treatment groups, week – 1 strata of HbA_{1c} (<8 or ≥8% [<64 or ≥64 mmol/mol]), metformin use (yes or no) strata at randomization, and country as fixed effects, and the corresponding baseline value as a covariate. Patients with both baseline and week 26 (LOCF) measurements are included. LOCF, last observation carried forward. *After a standardized meal in patients administered treatment before breakfast. †Weighted average of proportion difference between treatment groups from each strata (week – 1 strata of HbA_{1c} [<8.0 or ≥8.0%], randomization strata of metformin use) using Cochran–Mantel–Haenszel weights. ‡Prespecified end point. §$P < 0.0001$.

once- and thrice-daily arms (Table 2). Robust reductions in HbA_{1c}, as seen during the run-in period, continued in each of the treatment arms from the first study on-treatment measurement up to week 12 and remained relatively stable until the end of treatment at week 26 (Fig. 1*A*). Proportions of patients achieving glycemic targets are reported in Table 2. LS mean treatment difference in body weight change for lixisenatide versus insulin glulisine once daily was –1.7 kg (95% CI –2.26, –1.06). Contrary to treatment with lixisenatide, treatment with basal-plus and basal-bolus resulted in increased body weight from week 2 through week 26 (Fig. 1*B*). The percentage of patients with no weight gain over the course of study treatment was substantially higher with lixisenatide compared with the insulin glulisine once- and thrice-daily arms (Table 2).

At week 26, 7-point SMPG profiles were comparable for lixisenatide and insulin glulisine once daily, with glucose reductions observed after the evening meal and at bedtime (Fig. 1*C*). Reduction in glucose was also observed after lunch with insulin glulisine thrice-daily (Fig. 1*C*).

A larger proportion of patients treated with lixisenatide achieved the composite end points compared with insulin glulisine once daily and thrice daily. In particular, patients receiving lixisenatide were twice as likely to achieve the triple composite outcome of HbA_{1c} $<7\%$ (<53 mmol/mol) without weight gain or documented symptomatic hypoglycemia (Fig. 1*D*).

Safety

Hypoglycemia. Study investigators reported the percentage of patients with symptomatic hypoglycemia was higher in patients treated with insulin once daily or thrice daily versus lixisenatide ($P = 0.01$ and $P = 0.0001$, respectively) (Table 3). Compared with insulin glulisine once daily and thrice daily, a post hoc analysis showed that the rate of protocol-defined symptomatic hypoglycemia events was 25% and 51% lower, respectively, with lixisenatide (Table 3). Moreover, an exploratory analysis demonstrated that protocol-defined nocturnal hypoglycemia (from 2300 to <0600 h) was more common in both insulin glulisine arms versus lixisenatide (estimated rate ratios [95% CI] of 0.6 [0.4, 0.9] vs. 0.5 [0.3, 0.7] for lixisenatide vs. insulin glulisine once daily and thrice daily, respectively) (Table 3 and Fig. 1*E*). Serious symptomatic hypoglycemia was reported for two patients in the insulin glulisine once-daily arm versus none in the lixisenatide and insulin glulisine thrice-daily arms.

Overall Safety

A greater proportion of patients in the lixisenatide arm experienced gastrointestinal AEs compared with in the insulin glulisine arms (Table 3). Nausea and/or vomiting were the most common AEs in the lixisenatide arm (Table 3), resulting in treatment discontinuation in six patients. Gastrointestinal AEs resulted in 11 patients (4%) permanently discontinuing treatment in the lixisenatide arm compared with none in the insulin glulisine arms. Serious AEs were observed in similar numbers of patients in all treatment groups (lixisenatide, 11 of 298 [3.7%]; insulin glulisine once daily, 11 of 301 [3.7%]; insulin glulisine thrice daily, 14 of 294 [4.8%]).

Three patients died during study treatment; none of these events was adjudicated to be related to the investigational product. One patient in the lixisenatide arm was diagnosed with metastatic pancreatic cancer 35 days after the start of treatment and died after palliative care. Two patients in the insulin glulisine thrice-daily arm died: one of severe bleeding from a ruptured ankle ulcer and the other from exacerbation of chronic heart failure.

An investigator reported suspected pancreatitis in one patient in the lixisenatide arm on day 89. As a result, lixisenatide was temporarily discontinued. The symptoms subsequently disappeared, with no findings on imaging, and pancreatic enzyme levels returned to normal. Treatment with lixisenatide was resumed on day 102 and continued until the planned end-of-treatment visit, and routine assessment of pancreatic enzymes showed levels within the normal ranges. An independent review committee adjudicated this case as mild acute pancreatitis.

CONCLUSIONS

The GetGoal Duo-2 trial is the first trial to directly compare prandial lixisenatide with prandial insulin combined with basal insulin glargine and is also the first single head-to-head trial to compare a GLP-1 RA plus insulin glargine with both a basal-plus and a basal-bolus regimen. All three injectable options to advance basal insulin therapy provided substantial HbA_{1c} reductions but with meaningful clinical differences in treatment complexity and intensity of blood glucose monitoring, body weight changes, and, most notably, hypoglycemic risk. The findings of this study, therefore, provide an evidence-based framework for the decision-making process to select the appropriate treatment strategy on a patient-by-patient basis. The outcomes of this study were positive despite the testing on a very challenging, predominantly overweight and obese population with long-standing type 2 diabetes inadequately controlled on relatively high doses of basal insulin and receiving multiple OADs at study entry. Patients in all three treatment arms experienced substantial improvements in glucose control, but the lixisenatide arm also had reductions in body weight, fewer hypoglycemic events, and was a simpler regimen compared with the prandial insulin groups.

We propose that with so many effective glucose-lowering tools available, HbA_{1c} should no longer be viewed as the primary criterion for the assessment of treatment success or be the main basis upon which to make therapeutic decisions. Robust reductions in HbA_{1c} with prandial insulin can occur at the cost of substantial weight gain, increased occurrence of hypoglycemia, and greater treatment complexity with the additional burden and expense from the need for frequent insulin adjustments and blood glucose monitoring.

In contrast to the earlier GetGoal Duo-1 trial (10), patients included in GetGoal Duo-2 were not initiating basal insulin; rather, they had been receiving insulin treatment for several years at baseline, had more advanced disease, and most were overweight or obese. This challenging patient population and the use of two active comparator regimens in this trial highlight the scientific rigor of the study design and serve to underscore the robust nature of our results.

All of the coprimary end points were met: lixisenatide plus insulin glargine was noninferior for HbA_{1c} reductions versus basal-plus and basal-bolus and was statistically superior for changes in body weight compared with basal-bolus. Symptomatic hypoglycemia occurred in a

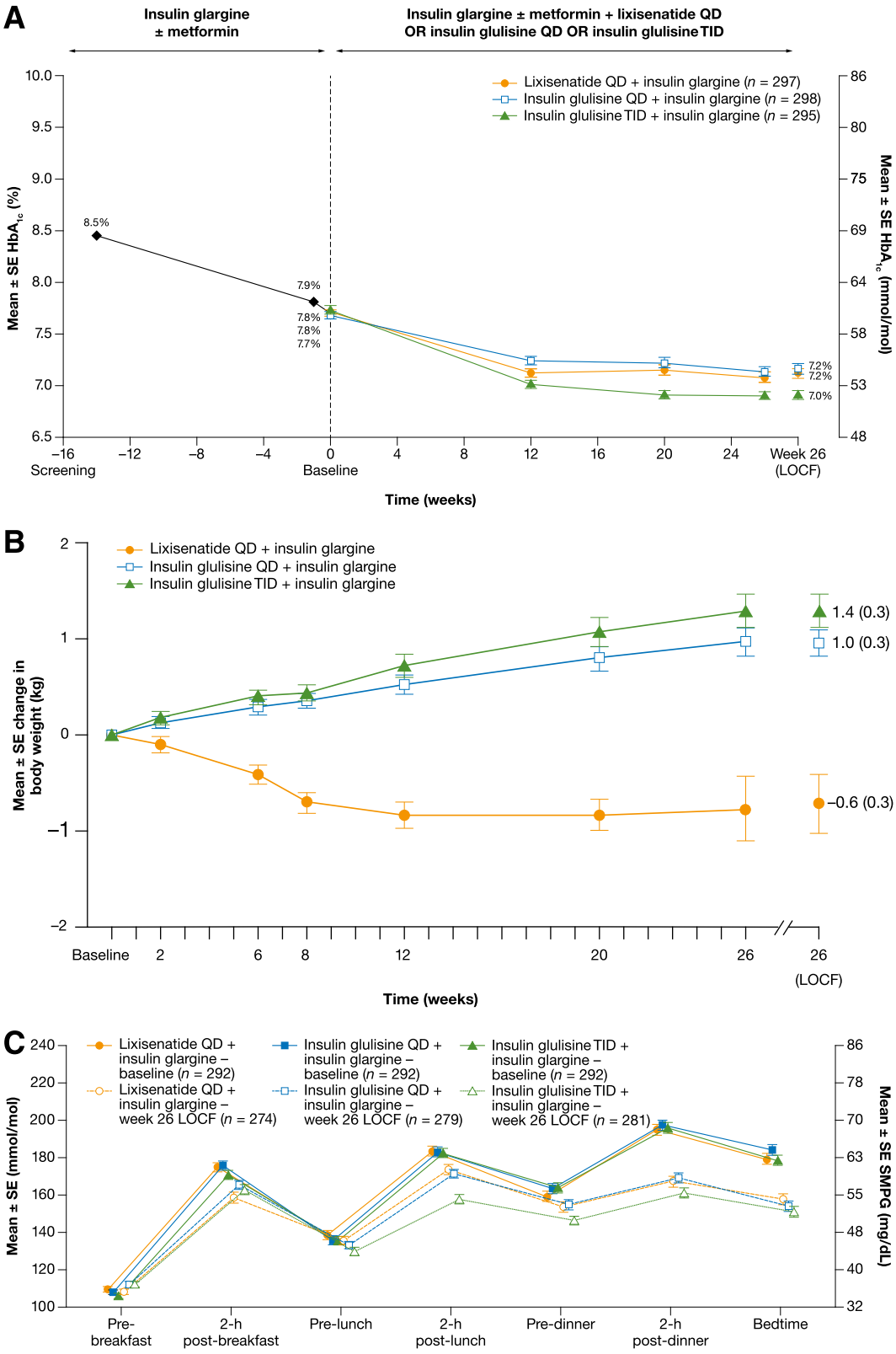

Figure 1—*A*: Change over time from baseline to week 26 (and last observation carried forward [LOCF]) for mean ± SE HbA_{1c} in the modified intent-to-treat (mITT) population. *B*: Change over time from baseline to week 26 (and LOCF) for mean ± SE body weight (mITT population). All treatment arms are with or without (±) metformin. *C*: Mean ± SE 7-point SMPG profiles at baseline and week 26 (mITT population). *D*: Patients achieving composite end points at week 26. *E*: Hypoglycemia events by hour of the day at week 26 (safety population). Data for symptomatic hypoglycemia per protocol (glucose <3.3 mmol/L [<60 mg/dL]/recovery with oral carbohydrate if no glucose measurement available). All treatment arms with or without metformin; 70% of patients receiving lixisenatide or insulin glulisine once daily (QD) administered their dose in the evening. TID, thrice daily.

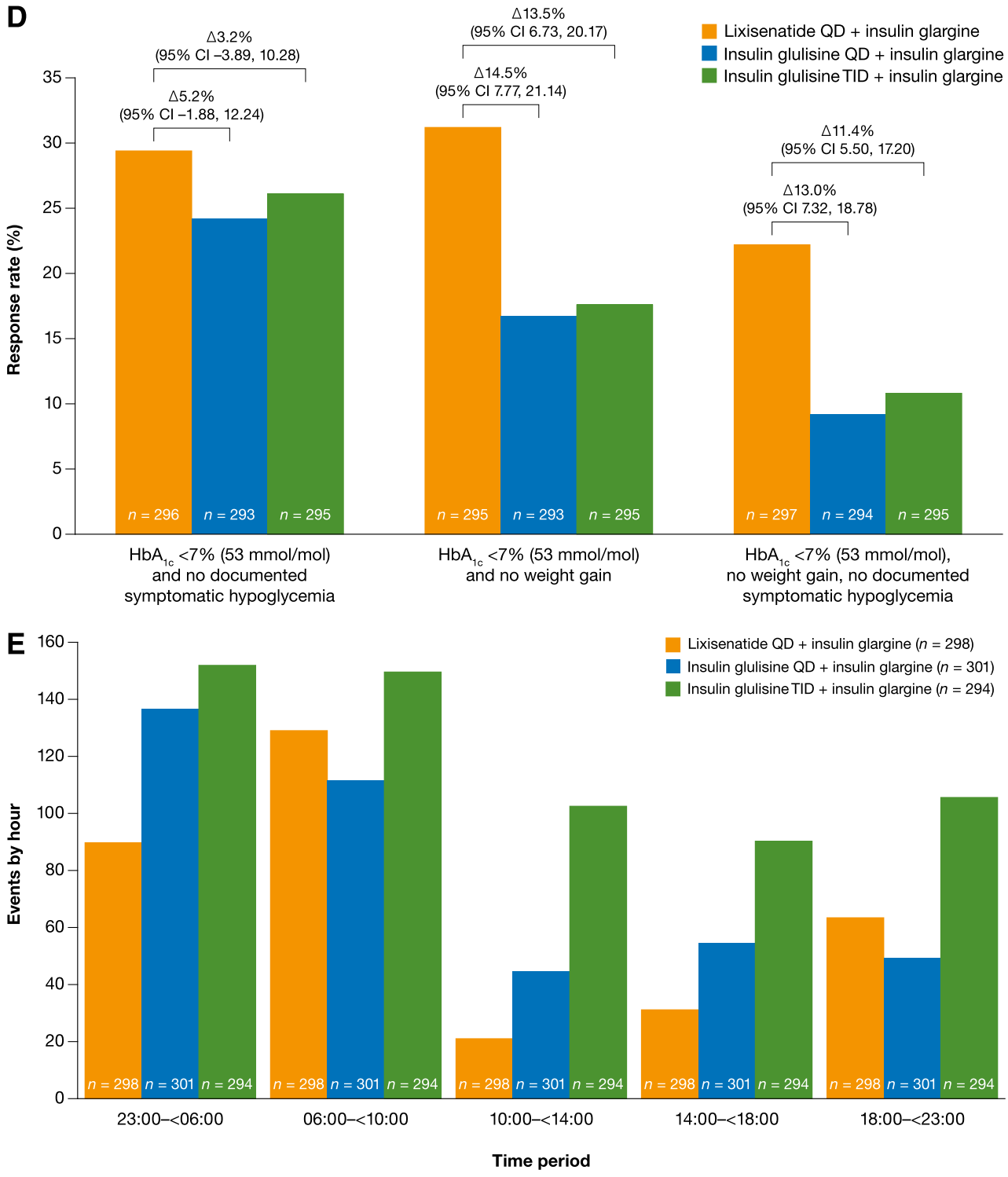

Figure 1—*Continued.*

higher proportion of patients in the basal-plus and basal-bolus arms than in the lixisenatide plus insulin glargine arm, and nocturnal hypoglycemic events were more frequent with insulin glulisine once daily or thrice daily than with lixisenatide. The negative effect of hypoglycemia in patients with type 2 diabetes in general, and particularly in patients of longer type 2 diabetes duration or older age (14), underscores the necessity of treatment individualization and highlights a need to consider the benefit-to-risk ratio of any new regimen.

Although the rate of AEs and serious AEs was comparable across the lixisenatide plus insulin glargine, basal-plus, and basal-bolus groups, as expected, GLP-1 RA class-associated gastrointestinal AEs, predominantly nausea but also vomiting and diarrhea, were more common in the lixisenatide plus insulin glargine group. This resulted in a higher but still relatively small number of

Table 3—Summary of patients experiencing AEs: safety population

Safety parameter	Lixisenatide 20 μg once daily (*n* = 298)	Insulin glargine with or without metformin plus: Insulin glulisine once daily (*n* = 301)	Insulin glargine with or without metformin plus: Insulin glulisine thrice daily (*n* = 294)
Any treatment-emergent AE	221 (74.2)	222 (73.8)	236 (80.3)
Any serious treatment-emergent AE	11 (3.7)	11 (3.7)	14 (4.8)
Treatment-emergent AE			
Leading to death	1 (0.3)	0	2 (0.7)
Leading to permanent discontinuation	15 (5.0)	2 (0.7)	3 (1.0)
Gastrointestinal AEs (system organ class and preferred term)	105 (35.2)	26 (8.6)	22 (7.5)
Nausea	75 (25.2)	5 (1.7)	3 (1.0)
Vomiting	26 (8.7)	5 (1.7)	6 (2.0)
Diarrhea	20 (6.7)	10 (3.3)	4 (1.4)
Pancreatic enzyme increase**			
Amylase	0	0	0
Lipase	2 (0.7)	1 (0.3)	3 (1.0)
Hypoglycemia			
Symptomatic hypoglycemia*	107 (35.9)	140 (46.5)†	154 (52.4)‡
Symptomatic hypoglycemia per protocol§	98 (32.9)	117 (38.9)	132 (44.9)‖
Symptomatic hypoglycemia events per protocol, *N*¶	332	395	600
Events by hour of the day			
2300 to <0600	89	136	151
0600 to <1000	128	111	149
1000 to <1400	21	44	102
1400 to <1800	31	54	90
1800 to <2300	63	49	105
Missing	0	1	3
Severe symptomatic hypoglycemia#	0	2 (0.7)	0
Exploratory analysis			
Estimated rate ratio lixisenatide-to-insulin glulisine for			
Symptomatic hypoglycemia events (95% CI)¶	–	0.75 (0.53, 1.06)	0.49 (0.34, 0.69)
Nocturnal symptomatic hypoglycemia (95% CI)¶	–	0.58 (0.37, 0.90)	0.47 (0.30, 0.73)

All data are *n* (%) patients with events, unless otherwise stated. **Defined as more than twice the upper limit of normal confirmed by repeat measurement. *Any symptomatic hypoglycemia reported as clinically meaningful by the study investigator regardless of plasma glucose. †$P = 0.01$ vs. lixisenatide (Fisher exact test; post hoc analysis). ‡$P = 0.0001$ vs. lixisenatide (Fisher exact test; post hoc analysis). §Symptomatic hypoglycemia accompanied by glucose <3.3 mmol/L (<60 mg/dL) or prompt recovery with oral carbohydrate. ‖$P = 0.0031$ vs. lixisenatide (Fisher exact test; post hoc analysis). ¶Number of hypoglycemia events was analyzed using negative binomial regression with a log-link function and the logarithm of the time period for which a hypoglycemic episode was considered treatment-emergent as offset, with treatment, randomization strata of HbA_{1c}, randomization strata of metformin use, and country as fixed effects. #Plasma glucose <2.0 mmol/L (<36 mg/dL) or with prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration; 70% of patients receiving lixisenatide or insulin glulisine once daily administered their dose in the evening.

discontinuations overall with lixisenatide versus the prandial insulins. However, 90% completion was observed in the lixisenatide group, which is better than the completion rates seen in other GLP-1 RA trials (15–17).

Patients in the lixisenatide arm were twice as likely to achieve the prespecified triple-composite outcome of HbA_{1c} <7% (<53 mmol/mol) without weight gain or documented symptomatic hypoglycemia versus the insulin glulisine arms, confirming a previous meta-analysis (18) that used propensity score matching to indirectly compare the efficacy and safety of insulin glulisine once daily and lixisenatide once daily both as add-on to insulin glargine in 24-week randomized controlled trials.

A number of studies have directly compared the efficacy and safety of other GLP-1 RAs with basal-plus or basal-bolus, but none have compared both insulin tactics versus a GLP-1 RA in the same trial. In the 30-week 4B study, exenatide twice daily plus insulin glargine demonstrated noninferior HbA_{1c} reductions with benefits in body weight and significant reductions in nonnocturnal hypoglycemia versus insulin lispro basal-bolus in patients inadequately controlled on basal insulin and metformin with or without an SU (19). Baseline HbA_{1c} was slightly higher in the 4B study (~8.2% [~66 mmol/mol]) owing to less vigorous titration during the run-in period versus values in GetGoal Duo-2; however, the final HbA_{1c} level in both studies was the same (7.2% [55 mmol/mol]), albeit with lixisenatide once-daily dosing versus exenatide twice-daily dosing.

The 26-week Harmony 6 study of 566 patients inadequately controlled on insulin glargine, with or without metformin and/or pioglitazone, demonstrated noninferiority of albiglutide weekly plus insulin glargine versus insulin lispro and insulin glargine as basal-bolus in HbA_{1c} reductions. Insulin glargine was not optimally titrated before randomization in this study, and final HbA_{1c} levels were higher than in our study at 7.7 and 7.8% (61 and 62 mmol/mol) in the albiglutide and basal-bolus arms, respectively (20).

The 26-week BEGIN: VICTOZA ADD-ON study (an addendum study of 413 patients

in whom degludec treatment vs. insulin glargine failed [HbA_{1c} >7% (>53 mmol/mol)]) compared liraglutide once daily at the highest dose of 1.8 mg as add-on to titrated insulin degludec versus insulin aspart basal-plus (21). Baseline HbA_{1c} was ~7.7% (~61 mmol/mol) in BEGIN ADD-ON, and a final HbA_{1c} level of ~7.2% (~55 mmol/mol) was reported, similar to GetGoal Duo-2.

Emerging evidence suggests that GLP-1 RAs seem to be a more valuable alternative to prandial insulin on top of basal insulin. Because GLP-1 RA agents are found to have differentiating features, such as frequency of administration and differential effects on FPG and PPG, their use in combination therapy can be individualized further. The pronounced PPG reductions associated with lixisenatide make it particularly suitable for treatment intensification after basal insulin because this combination permits improvements in both PPG and FPG. Prandial GLP-1 RAs suppress glucagon and also delay gastric emptying, which reduces the rate of postmeal glucose absorption, resulting in robust PPG reductions associated with the meal after administration (7,22). Hence, future head-to-head studies comparing other GLP-1 RAs added to basal insulin would be of interest.

Limitations of the current study include the relatively short 26-week duration and the open-label design; however, blinding would have required additional injections to mimic the basal-bolus regimen, adding additional complexity to a study that already required ongoing titration of basal insulin.

The findings of the current study support a change to the current treatment paradigm (4). Historically, prandial insulins have been recommended as first-line intensification regimens on top of basal insulin (1). We suggest that the spectrum of potential benefits (consistent efficacy, weight reduction, lower risk of hypoglycemia, and less treatment complexity) associated with the use of GLP-1 RAs indicate that they should be considered as the first-line option to advance basal insulin therapy, with basal plus prandial insulin being reserved for patients who cannot tolerate GLP-1 RAs due to gastrointestinal AEs (4). Basal-bolus insulin therapy should be relegated to the minority of patients who do not respond to the other simpler injectable strategies. Lixisenatide as add-on to basal insulin represents a valuable alternative to treatment intensification with basal-plus or basal-bolus, with a lower risk of hypoglycemia and without body weight gain, and may become a preferred therapeutic option.

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