Efficacy and Safety of Dulaglutide Added Onto Pioglitazone and Metformin Versus Exenatide in Type 2 Diabetes in a Randomized Controlled Trial (AWARD-1)

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OBJECTIVE

To compare the efficacy and safety of dulaglutide, a once-weekly GLP-1 receptor agonist, with placebo and exenatide in type 2 diabetic patients. The primary objective was to determine superiority of dulaglutide 1.5 mg versus placebo in HbA_{1c} change at 26 weeks.

RESEARCH DESIGN AND METHODS

This 52-week, multicenter, parallel-arm study (primary end point: 26 weeks) randomized patients (2:2:2:1) to dulaglutide 1.5 mg, dulaglutide 0.75 mg, exenatide 10 μg, or placebo (placebo-controlled period: 26 weeks). Patients were treated with metformin (1,500–3,000 mg) and pioglitazone (30–45 mg). Mean baseline HbA_{1c} was 8.1% (65 mmol/mol).

RESULTS

Least squares mean ± SE HbA_{1c} change from baseline to the primary end point was −1.51 ± 0.06% (−16.5 ± 0.7 mmol/mol) for dulaglutide 1.5 mg, −1.30 ± 0.06% (−14.2 ± 0.7 mmol/mol) for dulaglutide 0.75 mg, −0.99 ± 0.06% (−10.8 ± 0.7 mmol/mol) for exenatide, and −0.46 ± 0.08% (−5.0 ± 0.9 mmol/mol) for placebo. Both dulaglutide doses were superior to placebo at 26 weeks (both adjusted one-sided $P < 0.001$) and exenatide at 26 and 52 weeks (both adjusted one-sided $P < 0.001$). Greater percentages of patients reached HbA_{1c} targets with dulaglutide 1.5 mg and 0.75 mg than with placebo and exenatide (all $P < 0.001$). At 26 and 52 weeks, total hypoglycemia incidence was lower in patients receiving dulaglutide 1.5 mg than in those receiving exenatide; no dulaglutide-treated patients reported severe hypoglycemia. The most common gastrointestinal adverse events for dulaglutide were nausea, vomiting, and diarrhea. Events were mostly mild to moderate and transient.

CONCLUSIONS

Both once-weekly dulaglutide doses demonstrated superior glycemic control versus placebo and exenatide with an acceptable tolerability and safety profile.

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A slide set summarizing this article is available online.

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Type 2 diabetes is characterized by progressive β-cell failure and insulin resistance, and intensification of treatment is usually required over time. The American Diabetes Association and European Association for the Study of Diabetes recommend metformin for initial drug therapy (1). If alternative or combination therapy is necessary, other oral agents such as a sulfonylurea, thiazolidinedione, and dipeptidyl peptidase-4 (DPP-4) inhibitor may be used (1). Although optimal second- and third-line agents have not been firmly established, when oral agents alone do not allow a patient to achieve glycemic control, injectable agents such as a GLP-1 receptor agonist may be used. Among the available GLP-1 receptor agonists, there are differences in duration of action, frequency of dosing, and efficacy and safety profiles (2–5).

Dulaglutide is a long-acting human GLP-1 receptor agonist in development as a once-weekly treatment for type 2 diabetes (6,7). The molecule comprises two identical disulfide-linked chains, each containing an N-terminal GLP-1 analog sequence covalently linked to a modified human IgG4 Fc fragment by a small peptide (6). In contrast to native GLP-1, dulaglutide is resistant to degradation by DPP-4 and is large in size, which slows absorption and reduces renal clearance. The molecular features result in a soluble formulation and a prolonged half-life of ~5 days, making it suitable for once-weekly subcutaneous administration. Dulaglutide exhibits GLP-1–mediated effects, including glucose-dependent potentiation of insulin secretion, inhibition of glucagon secretion, delay of gastric emptying, and weight loss.

It is important to understand the benefits and risks of dulaglutide relative to other GLP-1 receptor agonists with differing pharmacological and clinical profiles. The purpose of AWARD-1 (Assessment of Weekly AdministRation of LY2189265 [dulaglutide] in Diabetes-1) was to compare once-weekly dulaglutide to placebo and exenatide twice daily (referred to hereafter as exenatide) in patients with type 2 diabetes treated with maximally tolerated doses of metformin and pioglitazone. This study allows a direct comparison of the efficacy and safety profiles of a short-acting GLP-1 receptor agonist and a long-acting one with sustained GLP-1 activation. This information should be useful in making treatment decisions for individual patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Eligible patients at screening were ≥18 years of age with a BMI between 23 and 45 kg/m^2 and glycosylated hemoglobin A_{1c} (HbA_{1c}) between 7.0% and 11.0% (53–97 mmol/mol) on oral antihyperglycemic medication (OAM) monotherapy or between 7.0% and 10.0% (53–86 mmol/mol) on combination OAM therapy. Patients were excluded from the study if they were taking GLP-1 receptor agonists during the 3 months before screening or were on long-term insulin therapy. The protocol was approved by local institutional review boards, and all patients provided written informed consent before participation in the trial. The study was conducted in accordance with the Declaration of Helsinki guidelines on good clinical practices (8).

Eligible patients entered a lead-in period that lasted up to 12 weeks (Fig. 1*A*). During this period, previous OAMs other than metformin and pioglitazone were discontinued, and patients were uptitrated on a dual-OAM regimen of maximally tolerated metformin (1,500–3,000 mg/day; >2,550 mg/day allowed only in certain countries outside the U.S. per country label) and pioglitazone (30–45 mg/day). Patients were then stabilized for ~8 weeks before randomization, at which time a qualifying HbA_{1c} >6.5% was required for ongoing eligibility.

Patients were then randomized to one of four arms (2:2:2:1) of subcutaneous injections of once-weekly dulaglutide 1.5 mg or dulaglutide 0.75 mg, exenatide, or once-weekly placebo (Fig. 1*A*) according to a computer-generated random sequence using an interactive voice response system. Exenatide-treated patients received 5 μg BID for the first 4 weeks and 10 μg BID for the remainder of the study. After 26 weeks, placebo-treated patients were switched in a blinded fashion (1:1) to dulaglutide 1.5 mg or dulaglutide 0.75 mg (52-week data for these patients are included in separate analyses not reported here). Randomization was stratified by country. An add-on rescue therapy was allowed for patients who met prespecified criteria for severe, persistent hyperglycemia; a detailed description of the criteria for rescue therapy is provided in the Supplementary Data. In addition, patients who discontinued the study drug because of an adverse event were allowed to remain in the study for safety follow-up.

The primary outcome measure was change in HbA_{1c} from baseline to 26 weeks. Secondary efficacy measures were change in HbA_{1c} from baseline to 52 weeks, percentage of patients with HbA_{1c} <7.0% (53 mmol/mol) or ≤6.5% (48 mmol/mol), changes in central laboratory fasting serum glucose (FSG), 8-point self-monitored plasma glucose (SMPG) profiles, change in body weight, and β-cell function and insulin sensitivity indices (updated HOMA2).

Safety assessments included adverse events, hypoglycemic episodes, vital signs, electrocardiograms, serial collection of laboratory parameters (hematology, urinalysis, hepatobiliary analytes, renal analytes, pancreatic enzymes, and calcitonin), injection site reactions, and dulaglutide antidrug antibodies (ADAs). Adjudication of pancreatic events was performed by an independent clinical event classification group. The following events were adjudicated to assess for possible development of pancreatitis: investigator-reported pancreatitis, adverse events of serious or severe abdominal pain without known cause, and confirmed cases of asymptomatic elevations (three or more times the upper limit of normal) in pancreatic enzymes. Laboratory analyses were performed at a central laboratory (Quintiles). Immunogenicity testing was performed by BioAgilytix (Durham, NC) and Millipore (St. Louis, MO).

Hypoglycemia was defined as plasma glucose (PG) ≤70 mg/dL (≤3.9 mmol/L) and/or symptoms or signs attributable to hypoglycemia. Severe hypoglycemia was defined as an episode requiring the assistance of another person to actively administer therapy (9).

Statistical Analyses

The study was designed with 90% power to show superiority of dulaglutide versus placebo and 93% power for noninferiority versus exenatide on the change from baseline in HbA_{1c} at the 26-week primary end point with an SD of 1.3%, a one-sided α of 0.025, and a

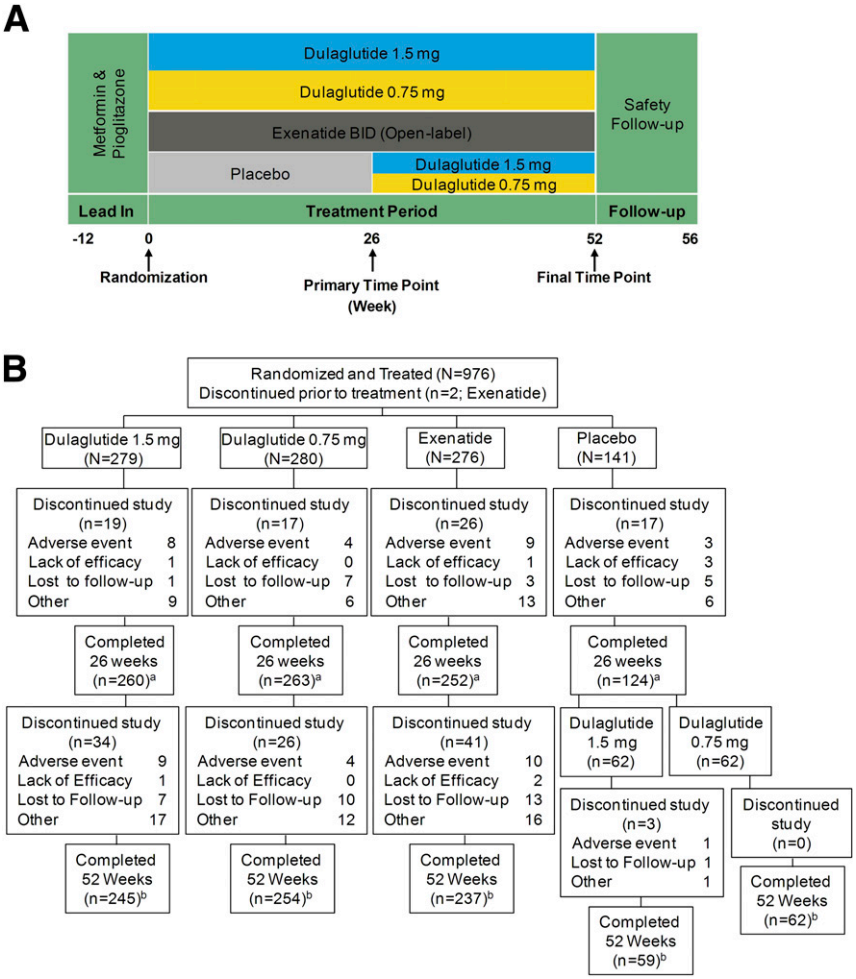

Figure 1—Study design (*A*) and patient disposition (*B*). All patients underwent a metformin (1,500–3,000 mg/day) and pioglitazone (30–45 mg/day) lead-in period that lasted up to 12 weeks and was continued for the duration of the study; other OAMs were discontinued. Two doses of dulaglutide (1.5 mg and 0.75 mg) were evaluated along with exenatide and placebo. Placebo patients continued until week 26 and were then randomized to dulaglutide 1.5 mg or dulaglutide 0.75 mg. [a]Number of patients rescued at week 26: dulaglutide 1.5 mg, 4 (1.4%); dulaglutide 0.75 mg, 12 (4.3%); exenatide, 11 (4.0%); placebo, 22 (15.6%). [b]Number of patients rescued at week 52: dulaglutide 1.5 mg, 9 (3.2%); dulaglutide 0.75 mg, 25 (8.9%); exenatide, 24 (8.7%); placebo to dulaglutide 1.5 mg, 1 (1.6%); placebo to dulaglutide 0.75 mg, 3 (4.8%).

noninferiority margin of 0.40%. This corresponds to 280 patients per active treatment arm and 140 for placebo, with an assumed dropout rate of 11%. The type I error rate across all treatment comparisons for change from baseline in HbA_{1c} at 26 weeks was controlled at 0.025 (one-sided) by tree gatekeeping (10). *P* values were adjusted so that each could be compared with 0.025 to assess significance while accounting for multiplicity adjustments (11).

The analyses of efficacy and safety were based on the intent-to-treat population comprising all randomized patients who received at least one dose of study treatment. For the assessment of efficacy and hypoglycemia events, only data collected before the initiation of rescue medication were used.

The change from baseline in HbA_{1c} and weight at 26 and 52 weeks were analyzed by ANCOVA, with factors for treatment, country, and baseline value as covariates. The last observation carried forward (LOCF) was used in the case of missing data. Secondary analysis methods for HbA_{1c} and weight and methods for other continuous secondary end points over time included a mixed-effects, repeated-measures (MMRM) analysis, with additional factors for visit and treatment-by-visit interaction and the patient as a random effect. Least squares (LS) means and SEs are reported. The percentage of patients achieving HbA_{1c} targets (LOCF) was analyzed by using a logistic regression model, with treatment, country, and baseline as covariates. Total hypoglycemia included events that were documented symptomatic, documented asymptomatic, probable, and/or severe (9). The percentage of patients experiencing adverse events was analyzed by using a χ^2 test unless there were no sufficient data to meet the assumptions of the analysis, in which case a Fisher exact test was conducted. The two-sided significance level was 0.05 for secondary end points and 0.10 for interactions.

RESULTS

A total of 978 patients were randomized to dulaglutide 1.5 mg, dulaglutide 0.75 mg, exenatide, and placebo. Two patients assigned to exenatide did not receive the drug; thus, the intention-to-treat population comprised 976 patients. Demographic and baseline characteristics were balanced across all arms (Table 1). At randomization, 86% of patients were receiving ≥2,500 mg/day of metformin and 45 mg/day of pioglitazone, and the mean doses were similar across arms. A total of 77 (7.9%) patients discontinued the study at 26 weeks; the distribution of patients across treatment arms was as follows: dulaglutide 1.5 mg, 19 (6.8%); dulaglutide 0.75 mg, 17 (6.1%); exenatide, 24 (8.7%); and placebo, 17 (12.1%). The most common reasons for study discontinuation at 26 weeks were adverse events and patient decision (Fig. 1*B*). Disposition, including patients receiving rescue therapy, throughout the 52-week study period is shown in Fig. 1*B*.

Efficacy

The LS mean ± SE HbA_{1c} change from baseline to the 26-week primary end point was −1.51 ± 0.06% (−16.5 ± 0.7 mmol/mol) for dulaglutide 1.5 mg, −1.30 ± 0.06% (−14.2 ± 0.7 mmol/mol) for dulaglutide 0.75 mg, −0.99 ± 0.06% (−10.8 ± 0.7 mmol/mol) for exenatide, and −0.46 ± 0.08% (−5.0 ± 0.9 mmol/mol) for placebo (Fig. 2*A*). Dulaglutide 1.5 mg and dulaglutide 0.75 mg were superior to placebo (LS mean difference; nominal 95% CI: −1.05% [−11.5 mmol/mol]; −1.22 to −0.88% [−13.3 to −9.6 mmol/mol] vs. −0.84% [−9.2 mmol/mol]; −1.01 to

Table 1—Baseline characteristics and demographics of patients

Variable	Dulaglutide 1.5 mg (*n* = 279)	Dulaglutide 0.75 mg (*n* = 280)	Exenatide (*n* = 276)	Placebo (*n* = 141)
Sex				
Male	163 (58)	168 (60)	156 (57)	83 (59)
Female	116 (42)	112 (40)	120 (44)	58 (41)
Age (years)	56 ± 10	56 ± 9	55 ± 10	55 ± 10
Race				
Hispanic or Latino	93 (33)	102 (36)	91 (33)	45 (32)
Not Hispanic or Latino	186 (67)	178 (64)	184 (67)	96 (68)
American Indian	40 (14)	37 (13)	38 (14)	20 (14)
Asian	6 (2)	8 (3)	4 (1)	6 (4)
Black	24 (9)	24 (9)	18 (7)	10 (7)
Multiple	3 (1)	3 (1)	3 (1)	2 (1)
Native Hawaiian	1 (<1)	1 (<1)	1 (<1)	0 (0)
White	205 (74)	207 (74)	211 (76)	103 (73)
BMI (kg/m^2)	33 ± 5	33 ± 6	34 ± 5	33 ± 6
Weight	96 ± 20	96 ± 21	97 ± 19	94 ± 19
Diabetes duration (years)	9 ± 6	9 ± 5	9 ± 6	9 ± 6
HbA_{1c} (%)	8.1 ± 1.3	8.1 ± 1.2	8.1 ± 1.3	8.1 ± 1.3
HbA_{1c} (mmol/mol)	65 ± 14	65 ± 13	65 ± 14	65 ± 14
FPG (mg/dL)	162 ± 56	159 ± 50	164 ± 55	166 ± 54
OAM treatment[a]				
1 OAM	55 (20)	67 (24)	76 (27)	44 (31)
2 OAMs	155 (56)	142 (51)	135 (49)	62 (44)
>2 OAMs	63 (23)	67 (24)	66 (24)	33 (23)
SBP (mmHg)	127 ± 15	127 ± 15	127 ± 15	125 ± 14
DBP (mmHg)	81 ± 9	77 ± 10	77 ± 10	77 ± 11

Data are mean ± SD or *n* (%) unless otherwise indicated. DBP, diastolic blood pressure; SBP, systolic blood pressure. [a]At screening.

−0.67% [−11.0 to −7.3 mmol/mol], respectively). Compared with exenatide, the mean changes from baseline were superior with dulaglutide 1.5 mg (−0.52% [−5.7 mmol/mol]; −0.66 to −0.39% [−7.2 to −4.3 mmol/mol]) and with dulaglutide 0.75 mg (−0.31% [−3.4 mmol/mol]; −0.44 to −0.18% [−4.8 to −2.0 mmol/mol]).

The LS mean HbA_{1c} changes from baseline to 52 weeks were −1.36 ± 0.08% (−14.9 ± 0.9 mmol/mol) for dulaglutide 1.5 mg, −1.07 ± 0.08% (−11.7 ± 0.9 mmol/mol) for dulaglutide 0.75 mg, and −0.80 ± 0.08% (−8.8 ± 0.9 mmol/mol) for exenatide (Fig. 2*A*). Compared with exenatide, the LS mean changes from baseline were superior for dulaglutide 1.5 mg (−0.56% [−6.1 mmol/mol]) and dulaglutide 0.75 mg (−0.27% [−3.0 mmol/mol]; adjusted $P < 0.001$, both comparisons). Figure 2*B* shows HbA_{1c} values at baseline and over time up to 52 weeks.

At 26 weeks, the percentage of patients attaining the HbA_{1c} goal of <7.0% (53 mmol/mol) was significantly higher in the dulaglutide 1.5-mg and dulaglutide 0.75-mg arms (78% and 66%, respectively) compared with exenatide (52%) ($P < 0.001$, both comparisons) and placebo (43%) ($P < 0.001$, both comparisons) (Fig. 2*C*). At the same time point, 63% and 53% of patients receiving dulaglutide 1.5 mg and dulaglutide 0.75 mg, respectively, achieved an HbA_{1c} target of ≤6.5% (48 mmol/mol) compared with 38% in the exenatide arm and 24% in the placebo arm ($P < 0.001$, all comparisons). At 52 weeks, 57% and 48% of the dulaglutide 1.5-mg and dulaglutide 0.75-mg patients, respectively, achieved this target, compared to 35% in the exenatide arm (Fig. 2*C*).

The majority of effects on FSG (measured by the central laboratory) were observed within 2 weeks after randomization for all active treatment arms and remained steady thereafter (Fig. 2*D*). The LS mean FSG changes from baseline to 26 weeks were −43 ± 2 mg/dL for dulaglutide 1.5 mg, −34 ± 2 mg/dL for dulaglutide 0.75 mg, −24 ± 2 mg/dL for exenatide, and −5 ± 3 mg/dL for placebo. All active treatment arms were associated with a greater decrease in FSG compared with placebo. LS mean differences between dulaglutide 1.5 mg and dulaglutide 0.75 mg versus exenatide were −18 mg/dL and −10 mg/dL, respectively ($P < 0.001$, both comparisons). At 52 weeks, both dulaglutide arms continued with significantly greater changes from baseline in FSG compared with exenatide ($P < 0.001$, dulaglutide 1.5 mg; $P = 0.005$, dulaglutide 0.75 mg) (Fig. 2*D*).

Figure 2*E* shows the mean of each PG value from the 8-point SMPG profile at baseline and 26 weeks. The analysis of changes in the individual components of the daily blood glucose profile demonstrated that dulaglutide 1.5 mg and dulaglutide 0.75 mg were associated with a greater reduction in the mean of all premeal PG compared with placebo and exenatide ($P < 0.001$, both comparisons). All active treatment arms had significantly greater LS mean reductions in postprandial PG compared with placebo ($P < 0.001$, all comparisons). Patients receiving dulaglutide 1.5 mg had a significantly greater reduction in the mean of all postprandial PG values compared with exenatide ($P = 0.047$). Patients receiving dulaglutide 1.5 mg and exenatide demonstrated greater reductions in the mean of all 2-h postprandial PG excursions compared with placebo ($P = 0.003$, dulaglutide 1.5 mg; $P < 0.001$, exenatide), with changes in the exenatide group significantly greater than in the dulaglutide groups ($P < 0.001$, both comparisons). All three active treatment arms exhibited similar reductions in the morning meal postprandial PG. Compared with exenatide at the midday meal, LS mean reductions in postprandial PG were significantly greater for dulaglutide 1.5 mg and dulaglutide 0.75 mg ($P < 0.001$ and $P = 0.049$, respectively). At the evening meal, LS mean reduction in postprandial PG was significantly greater for dulaglutide 1.5 mg than for exenatide ($P = 0.044$). Results were similar for active treatment arms at 52 weeks (data not shown).

The LS mean change in body weight (ANCOVA LOCF) from baseline to 26 weeks was −1.30 ± 0.29 kg for dulaglutide 1.5 mg, 0.20 ± 0.29 kg for dulaglutide 0.75 mg, −1.07 ± 0.29 kg for exenatide, and 1.24 ± 0.37 kg for placebo (Fig. 2*F*). Compared with placebo, change in weight with dulaglutide 1.5 mg, dulaglutide 0.75 mg, and exenatide was significantly different ($P < 0.001$,

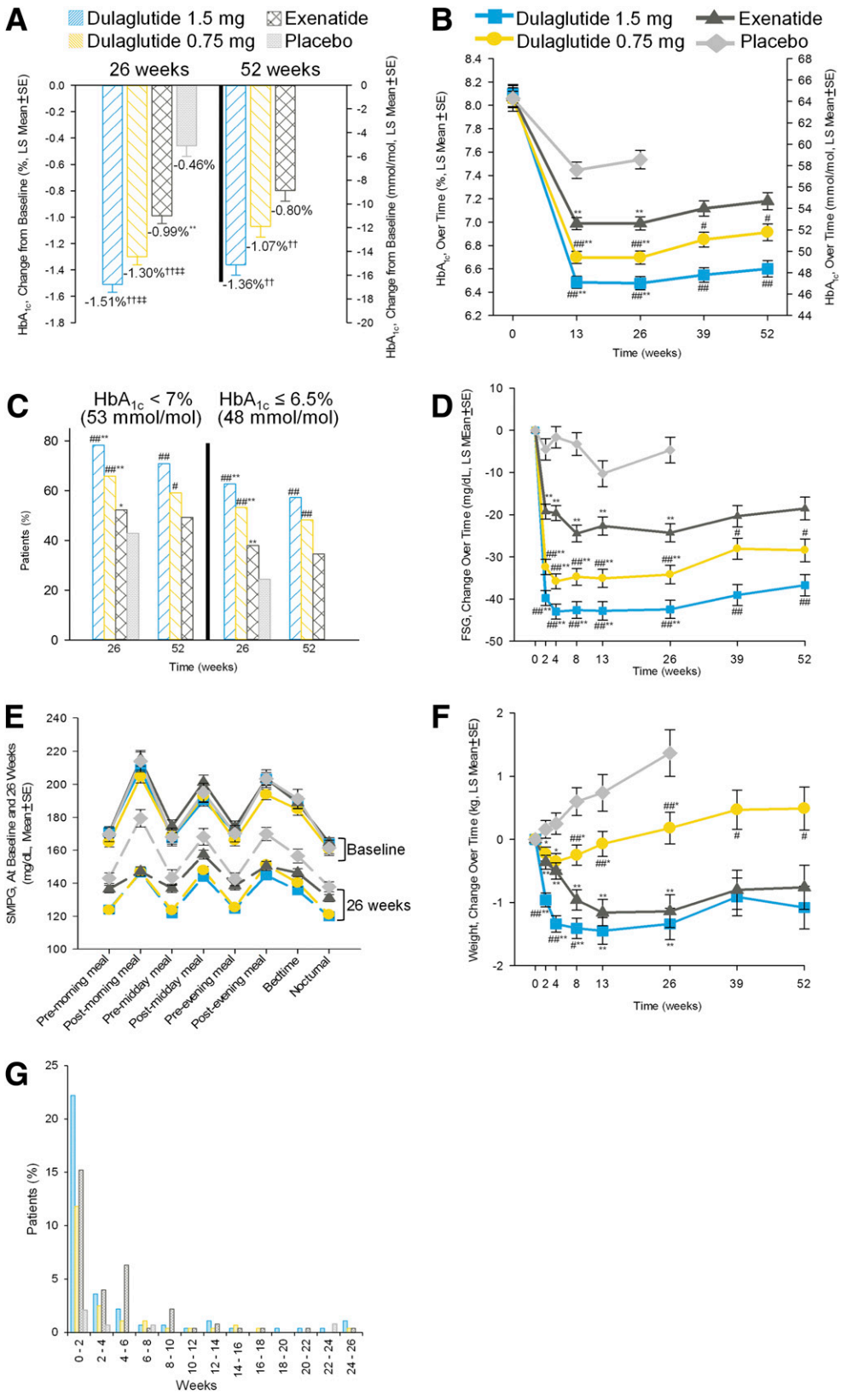

Figure 2—Efficacy and safety measures through the treatment period. *A*: Change in HbA_{1c} from baseline at 26 and 52 weeks, ANCOVA LOCF. *B*: HbA_{1c} over time, MMRM. *C*: Percentage of patients achieving HbA_{1c} targets, logistic regression. *D*: Change in FSG over time, MMRM. *E*: Baseline and 26-week 8-point SMPG profiles, MMRM (solid lines are baseline, and dashed lines are at 26 weeks). *F*: Change in weight over time, MMRM. *G*: Incidence of nausea up to 26 weeks. Data are LS mean ± SE. ††$P < 0.001$, superiority vs. exenatide; ‡‡$P < 0.001$, superiority vs. placebo; #$P <$ 0.05 vs. exenatide; *$P < 0.05$ vs. placebo; ##$P < 0.001$ vs. exenatide; **$P < 0.001$ vs. placebo.

$P = 0.010$, and $P < 0.001$, respectively). Compared with exenatide, the decrease in body weight was similar for dulaglutide 1.5 mg, and there was significantly greater weight gain for dulaglutide 0.75 mg (LS mean difference: −0.24 kg [$P = 0.474$] for dulaglutide 1.5 mg, 1.27 kg [$P < 0.001$] for dulaglutide 0.75 mg). The observed differences in weight between the dulaglutide groups and the exenatide group were maintained at 52 weeks (Fig. 2*F*).

Pancreatic β-cell function, as measured by HOMA2-%B at 26 weeks, increased with all active treatment arms compared with placebo and increased more with dulaglutide 1.5 mg than with exenatide ($P < 0.001$, all comparisons). At 52 weeks, both dulaglutide arms had higher HOMA2-%B values versus exenatide ($P < 0.001$, both comparisons). No differences were observed among the arms with respect to insulin sensitivity estimated by HOMA2-%S (Supplementary Table 1). Patients treated with dulaglutide 1.5 mg demonstrated a significant mean reduction from baseline in total and LDL cholesterol levels compared with placebo at 26 weeks (Supplementary Table 1). These patients also demonstrated a significant reduction in mean triglyceride levels compared with exenatide at 26 and 52 weeks and placebo at 26 weeks. No differences were observed among arms for change from baseline in mean HDL cholesterol levels.

Safety

The incidence of serious adverse events was similar across treatment arms (Table 2). Two patients died during the study (one of myocardial infarction in the dulaglutide 1.5 mg arm and one of natural causes in the dulaglutide 0.75 mg arm [patient had a history of cardiovascular risk factors]) at 90 and 102 days postrandomization, respectively. One patient who received dulaglutide 1.5 mg for 6 months died of pancreatic cancer 9 months after discontinuation from the study.

The incidence of adverse events was similar across arms (Table 2). Gastrointestinal adverse events, including nausea, vomiting, and diarrhea, were the most commonly reported in dulaglutide- and exenatide-treated patients; nausea and vomiting events were significantly ($P < 0.05$, all comparisons) higher in dulaglutide- and exenatide-treated patients than in placebo-treated patients at 26 weeks. The incidence of these events was similar among patients receiving dulaglutide 1.5 mg and exenatide and

Table 2—Safety assessments, change from baseline in vital signs, and TE dulaglutide ADAs

	26 weeks				52 weeks		
Variable	Dulaglutide 1.5 mg (*n* = 279)	Dulaglutide 0.75 mg (*n* = 280)	Exenatide (*n* = 276)	Placebo (*n* = 141)	Dulaglutide 1.5 mg (*n* = 279)	Dulaglutide 0.75 mg (*n* = 280)	Exenatide (*n* = 276)
Death	1 (0.4)	1 (0.4)	0 (0)	0 (0)	1 (0.4)	1 (0.4)	0 (0)
Serious AEs, *n* (%)	12 (4)	15 (5)	15 (5)	12 (9)	18 (7)	22 (8)	27 (10)
AEs (patients with ≥1 event)	215 (77)	199 (71)	198 (72)	104 (74)	226 (81)	220 (79)	221 (80)
TE AEs (≥5% patients)							
GI events	131 (47)**	83 (30)#*	117 (42)**	26 (18)	142 (51)	94 (34)#	128 (46
Nausea	78 (28)**	45 (16)#*	71 (26)**	8 (6)	81 (29)	47 (17)#	77 (28)
Vomiting	47 (17)#**	17 (6)#*	30 (11)**	2 (1)	47 (17)	17 (6)#	33 (12)
Diarrhea	31 (11)	22 (8)	16 (6)	8 (6)	36 (13)	26 (9)	21 (8)
Dyspepsia	22 (8)*	5 (2)#	19 (7)	4 (3)	23 (8)	6 (2)#	20 (7)
Constipation	12 (4)	5 (2)	5 (2)	2 (1)	16 (6)#	5 (2)	5 (2)
Flatulence	14 (5)	3 (1)	6 (2)	3 (2)	16 (6)	3 (1)	7 (3)
Infections and infestations	74 (27)	74 (26)	78 (28)	43 (31)	110 (39)	101 (36)	107 (39)
Nasopharyngitis	18 (7)	23 (8)	12 (4)	8 (6)	27 (10)	26 (9)	16 (6)
URI	12 (4)	14 (5)	12 (4)	6 (4)	15 (5)	23 (8)	19 (7)
UTI	12 (4)	8 (3)	7 (3)	4 (3)	17 (6)	13 (5)	13 (5)
Headache	20 (7)	9 (3)	24 (9)	8 (6)	26 (9)	14 (5)	24 (9)
Fatigue	10 (4)#	12 (4)	21 (8)*	2 (1)	13 (5)	13 (5)	22 (8)
Decreased appetite	22 (8)#*	14 (5)	8 (3)	3 (2)	23 (8)#	15 (5)	9 (3)
Peripheral edema	3 (1)	13 (5)	11 (4)	7 (5)	8 (3)	15 (5)	17 (6)
Back pain	11 (4)	9 (3)	8 (3)	9 (6)	15 (5)	13 (5)	12 (4)
Dizziness	15 (5)	8 (3)#	18 (7)*	2 (1)	18 (7)	9 (3)	21 (8)
Arthralgia	8 (3)	10 (4)	9 (3)	3 (2)	10 (4)	16 (6)	13 (5)
Pain in extremity	6 (2)	8 (3)	8 (3)	6 (4)	11 (4)	13 (5)	13 (5)
Discontinuation due to AE	8 (3)	4 (1)	9 (3)	3 (2)	9 (3)	4 (1)	10 (4)
Safety parameters							
SBP (mmHg)	0.11 ± 0.83*	−0.36 ± 0.82*	0.06 ± 0.83*	3.40 ± 1.13	0.83 ± 0.87	1.62 ± 0.85	0.02 ± 0.88
DBP (mmHg)	0.76 ± 0.55	0.56 ± 0.54	−0.11 ± 0.55	1.25 ± 0.75	0.89 ± 0.57	0.76 ± 0.57	0.02 ± 0.58
Heart rate (beats/min)	2.80 ± 0.52#*	2.80 ± 0.51#*	1.18 ± 0.52	0.61 ± 0.70	1.68 ± 0.56	1.56 ± 0.55	1.15 ± 0.56
TE ADAs							
Dulaglutide ADAs	4 (1.4)	2 (0.7)	12 (4.3)	2 (1.4)	5 (1.8)	3 (1.1)	14 (5.1)
Exenatide ADAs	—	—	75 (27.2)	—	—	—	58 (21.0)

Data are *n* (%) and LS mean ± SE. AE, adverse event; DBP, diastolic blood pressure; GI, gastrointestinal; SBP, systolic blood pressure; TE, treatment emergent; URI, upper respiratory infection; UTI, urinary tract infection. **$P < 0.001$ vs. placebo. #$P < 0.05$ vs. exenatide. *$P < 0.05$ vs. placebo.

significantly ($P < 0.05$, all comparisons) lower in those receiving dulaglutide 0.75 mg after 52 weeks. The majority of the events were mild to moderate in severity. Nausea was primarily transient, with new-onset cases occurring primarily in the first 2 weeks of treatment with both doses of dulaglutide (Fig. 2*G*).

Discontinuations due to adverse events were similar across treatment arms at 26 and 52 weeks (Fig. 1*B*). The most common adverse event leading to discontinuation was nausea (three for dulaglutide 1.5 mg, one for dulaglutide 0.75 mg, and four for exenatide). One patient from the dulaglutide 1.5 mg arm was given a diagnosis of chronic pancreatitis ~7 months after study drug initiation. This patient had no signs or symptoms of pancreatitis before study initiation but had transient elevations in pancreatic enzymes starting at baseline and continuing throughout the study, including during the 6 months after study drug discontinuation when the patient was allowed to remain in the study but off the study drug.

A total of 108 patients (dulaglutide 1.5 mg, 10.4%; dulaglutide 0.75 mg, 10.7%; exenatide, 15.9%; placebo, 3.5%) experienced hypoglycemia during the first 26 weeks, with significantly fewer patients in the dulaglutide 1.5 mg arm compared with the exenatide arm ($P = 0.007$). The mean 1-year adjusted rates of total hypoglycemia were 0.45, 1.10, 1.47, and 0.37 events/patient/year for dulaglutide 1.5 mg, dulaglutide 0.75 mg, exenatide, and placebo, respectively, at 26 weeks. The incidences and rates of total hypoglycemia remained lower for dulaglutide 1.5 mg than for exenatide at 52 weeks. There were no events of severe hypoglycemia among dulaglutide-treated patients, and two events were reported for exenatide-treated patients.

Small median increases in serum lipase, total amylase, and pancreatic amylase (p-amylase) that remained within normal range were observed for dulaglutide and exenatide; these changes were significant ($P < 0.05$, all comparisons) compared with placebo (Supplementary Table 1). Increases in pancreatic enzymes were greater for dulaglutide 1.5 mg than for exenatide at 26 weeks and were greater for total amylase and p-amylase at 52 weeks. Incidences of treatment-emergent values above the upper limit of normal for pancreatic enzymes were similar for the active treatments compared with placebo at 26 weeks and among the active treatments at 52 weeks (Supplementary Table 1). Calcitonin values remained stable throughout the study in all treatment arms.

There were no clinically relevant changes in LS mean systolic blood pressure among the three active treatment arms at 26 or 52 weeks (Table 2); in the placebo group, there was an increase in systolic blood pressure of 3.40 mmHg. There were no differences observed among arms for change in diastolic blood pressure at 26 or 52 weeks (Table 2). Dulaglutide 1.5 mg and dulaglutide 0.75 mg were associated with significantly ($P < 0.05$, all comparisons) greater LS mean increases in heart rate at 26 weeks compared with exenatide and placebo; no differences between dulaglutide and exenatide were noted at 52 weeks (Table 2).

Ten (1.8%) patients randomized to dulaglutide developed treatment-emergent dulaglutide ADAs at least once postbaseline during the 52-week study (Table 2). Another three patients who were randomized to placebo developed treatment-emergent dulaglutide ADAs after switching to dulaglutide at 26 weeks. One patient treated with dulaglutide 1.5 mg with a treatment-emergent dulaglutide ADA experienced local injection site erythema and swelling for 1 day. In exenatide-treated patients at 26 weeks, 48% were noted to have treatment-emergent exenatide ADAs (Table 2) of whom one experienced an injection site reaction. No patients reported systemic hypersensitivity reactions.

CONCLUSIONS

The results of the AWARD-1 study demonstrate that once-weekly dulaglutide in combination with maximally tolerated doses of metformin and pioglitazone results in significantly larger improvements in HbA_{1c} and percentages of patients achieving target HbA_{1c} goals compared with placebo and the active comparator exenatide at 26 weeks. Additionally, dulaglutide 1.5 mg was associated with significant weight reduction compared with placebo. Importantly, the clinically relevant mean difference in HbA_{1c} change from baseline between the dulaglutide and the exenatide arms of ~0.3%–0.5% was achieved with a similar or lower risk of hypoglycemia, indicating an acceptable benefit and hypoglycemic risk profile for this new, once-weekly GLP-1 receptor agonist.

At randomization, the majority (86%) of patients tolerated the uptitration to maximum approved doses of both metformin and pioglitazone and had a study-qualifying $HbA_{1c} > 6.5\%$ (48 mmol/mol) after 8 weeks of stabilization, demonstrating that the study was conducted in a patient population that was appropriate for the addition of a third antihyperglycemic agent. In this population, patients receiving dulaglutide 1.5 mg achieved a further 1.5% HbA_{1c} reduction from the baseline mean HbA_{1c} of 8.1% (65 mmol/mol), with 78% achieving the goal of <7.0% (53 mmol/mol); both results are superior to exenatide. The previously reported similar glycemic effect of dulaglutide (12) and exenatide (13,14) compared with placebo provides additional support for the current results.

The impact of dulaglutide and exenatide on glucose control was evident early in the course of therapy, with a near-maximal decrease in FSG observed as early as 2 weeks after the initiation of therapy and a significantly greater magnitude of effect with dulaglutide compared with exenatide. Although both GLP-1 receptor agonists improved preprandial and postprandial blood glucose control as measured on 8-point SMPG profiles, there were some notable differences. Changes from baseline in the mean of all preprandial and postprandial PG values were greater with dulaglutide relative to exenatide. Exenatide was associated with a smaller mean postprandial excursion compared with dulaglutide likely because of the higher absolute premeal glycemic level with exenatide. Glycemia is the main factor influencing insulin secretion rates in β-cells exposed to a GLP-1 receptor agonist; therefore, patients with near-normal glycemia require less insulin to be secreted after the meal to maintain blood glucose levels within the physiologic range, which is believed to result in the observed difference in glucose excursions in the current study.

Weight loss was similar for dulaglutide 1.5 mg and exenatide, despite the greater reduction of HbA_{1c} with

dulaglutide 1.5 mg and known weight effects of background thiazolidinedione therapy over time (15,16). Dulaglutide 0.75 mg did not have the same weight loss effect as dulaglutide 1.5 mg and exenatide, which may indicate a greater GLP-1 receptor agonist concentration requirement to achieve the weight loss observed with dulaglutide 1.5 mg. These results are consistent with the magnitude of weight loss observed in other studies evaluating GLP-1 receptor agonists on a background therapy of metformin and thiazolidinedione (17,18).

The safety profile of dulaglutide in this trial is generally consistent with the known effects of the GLP-1 receptor agonist class. Patients treated with dulaglutide 1.5 mg and exenatide reported similar incidences of gastrointestinal adverse events, with less frequent reporting by patients treated with dulaglutide 0.75 mg. The incidence of nausea and vomiting also appeared to be similar to the incidence observed with liraglutide when used with similar background therapy (18), with nausea reported by 29% and 40% of patients treated with liraglutide 1.2 mg and 1.8 mg and vomiting by 7% and 17%, respectively. Overall, fewer dulaglutide-treated patients experienced hypoglycemia compared with exenatide-treated patients. Cardiovascular assessments showed an increase in systolic blood pressure with placebo compared with the dulaglutide and exenatide arms, which may be partly a result of the increase in weight observed in the placebo arm. An increase in heart rate was observed with dulaglutide and exenatide and was similar to changes observed within the GLP-1 receptor agonist class (19,20). There were no clinical adverse events identified based on serial evaluations of thyroid and pancreatic laboratory parameters. The immunogenicity of dulaglutide appeared to be low, with $<$2% of patients developing treatment-emergent dulaglutide ADAs in contrast to a 47% incidence in patients treated with exenatide.

Limitations of the clinical application of these results include the unforeseen decrease in the use of high-dose thiazolidinedione therapy during the course of the study. During the lead-in period, there was forced titration of metformin and pioglitazone to maximally tolerated doses, which may not always be routine in clinical practice. The study was performed in Mexico, Argentina, and the U.S. in a population that was primarily white and Hispanic.

Overall, once-weekly dulaglutide therapy is efficacious and safe in combination with metformin and pioglitazone. Dulaglutide is superior to placebo and exenatide with respect to HbA_{1c} change from baseline and the percentage of patients achieving glycemic targets. Additionally, the observed rapid improvement in fasting glucose and SMPG values, with an attendant low risk of hypoglycemia, represents an important treatment profile in the management of patients with type 2 diabetes.

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SUPPLEMENTARY DATA

Supplementary Table 1. Other end points of interest, change from baseline to 26 and 52 weeks

	26 weeks				52 weeks		
	DU 1.5 mg (N=279)	DU 0.75 mg (N=280)	EX (N=276)	PL (N=141)	DU 1.5 mg (N=279)	DU 0.75 mg (N=280)	EX (N=276)
Insulin and HOMA Parameters							
Fasting Insulin (pmol/L)	7.3 (4.2)	1.9 (4.3)	3.0 (4.3)	-2.2 (5.9)	12 (4.5)	6.0 (4.6)	10 (4.7)
HOMA2-%B	36 (2.6)[##**]	24 (2.7)[#**]	15 (2.6)[**]	0.93 (3.7)	35 (2.6)[##]	26 (2.7)[##]	14 (2.8)
HOMA2-%S	-3.1 (2.9)	1.2 (3.0)	-1.6 (2.9)	2.6 (4.1)	-7.5 (2.9)	-5.5 (3.0)	-3.8 (3.1)
Lipid Parameters, mean ± SD (mmol/L)							
Cholesterol	-0.15 ± 0.82[*]	-0.10 ± 0.85	-0.05 ± 0.86[*]	0.04 ± 0.72	-0.12 ± 0.86	-0.09 ± 0.84	-0.01 ± 0.88
LDL	-0.11 ± 0.66[*]	-0.08 ± 0.73	-0.03 ± 0.73[*]	0.01 ± 0.62	-0.06 ± 0.69	-0.08 ± 0.77	-0.02 ± 0.75
HDL	0.04 ± 0.19	0.02 ± 0.19	0.02 ± 0.18	0.01 ± 0.22	0.05 ± 0.22	0.00 ± 0.20	0.02 ± 0.20
Triglycerides	-0.20 ± 1.16[#*]	-0.08 ± 0.76	-0.03 ± 1.04	0.11 ± 1.56	-0.26 ± 1.23[#]	0.04 ± 0.95	-0.03 ± 1.13
Pancreatic Enzymes, Median [Q1,Q3] (U/L)							
Lipase	19 [-4, 44][#**]	8 [-11,36][**]	8 [-7, 29][**]	-6 [-22, 17]	16 [-6, 40]	5 [-14, 27]	9 [-11, 37]
Total Amylase	7 [-1. 17][##**]	3 [-4,11][*]	3 [-4, 10][*]	-1 [-9, 8]	5 [-2, 13][##]	2 [-7, 10]	2 [-6, 9]
p-Amylase	4 [0, 11][##**]	3 [-1, 7][**]	2 [-1, 7][*]	0 [-3,5]	4 [1, 10][##]	2 [-2, 8]	2 [-2, 7]
Patients with TE, abnormal, n (%)[a]							
Lipase	46 (17)	37 (13)	29 (11)	10 (7)	85 (37)	86 (37)	74 (32)
Total Amylase	15 (6)	14 (5)	12 (4)	8 (6)	36 (14)	35 (14)	28 (11)
p-Amylase	24 (9)	17 (6)	17 (6)	8 (6)	51 (20)	45 (18)	41 (16)
Pancreatic Enzymes, n (%) of patients with ≥3x ULN[b]							
Lipase	8 (3.0)	6 (2.2)	7 (2.7)	2 (1.5)	10 (4.0)	6 (2.3)	5 (2.1)
p-Amylase	2 (0.8)	1 (0.4)	0 (0)	0 (0)	1 (0.4)	2 (0.8)	0 (0)

[a]Cumulative number (%) of patients with at least one treatment emergent abnormality. [b]Patients with a value ≥3x ULN during the time period assessed.

All data are LS mean ± SE unless otherwise noted. [#,*] $P < 0.05$ vs exenatide and placebo, respectively. [##,**] $P < 0.001$ vs exenatide and placebo, respectively. Abbreviations: DU = dulaglutide; EX = exenatide; HOMA2-%B = updated homeostasis model beta cell function; HOMA2-%S = updated homestasis model insulin sensitivity; p-amylase = pancreatic amylase; PL = placebo; Q1 = first quartile; Q3 = third quartile.

SUPPLEMENTARY DATA

Special Treatment Considerations for Management of Patients Who Did Not Attain HbA_{1c} Target and Patients with Severe, Persistent Hyperglycemia during the Treatment Period

An additional therapeutic intervention was considered in patients with a follow-up shorter than 6 months who developed persistent, severe hyperglycemia despite full compliance with the assigned therapeutic regimen. Persistent, severe hyperglycemia was defined as (a) average fasting blood glucose over at least a 2-week period (at least 4 values/week must be available) above 270 mg/dL at any time during the first 6 weeks after randomization, or above 240 mg/dL over at least a 2-week period (at least 4 values/week must be available) any time after the first 6 weeks postrandomization, or above 200 mg/dL at any time after the first 26 weeks; and (b) in the absence of any acute condition that raises blood glucose. If a patient develops persistent, severe hyperglycemia, but his most recent HbA_{1c} measurements indicate a significant improvement in glycemic control (HbA_{1c} change ≥0.3%) compared to the previous value, the investigator will decide if a new intervention is warranted.

Patients with persistent postrandomization HbA_{1c} values ≥8% (64 mmol/mol) (on 2 or more occasions at least 12 weeks apart) during the second 26 weeks of the treatment period should be considered for further therapeutic intervention.

Intervention was based on standards of care (17, 18), and was determined by the investigator, but the patients should have continued administering their allocated LY2189265 dose. The use of other incretin mimetics (for example, liraglutide or exenatide) was not permitted (other than study drug or those already randomized to exenatide).