Efficacy and Safety of Once-Weekly Dulaglutide Versus Insulin Glargine in Patients With Type 2 Diabetes on Metformin and Glimepiride (AWARD-2)

Francesco Giorgino,[1] Marian Benroubi,[2] Jui-Hung Sun,[3] Alan G. Zimmermann,[4] and Valeria Pechtner[5]

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OBJECTIVE

This study compared the efficacy and safety of once-weekly dulaglutide, a glucagon-like peptide-1 receptor agonist, with daily insulin glargine, both combined with maximally tolerated doses of metformin and glimepiride in patients with type 2 diabetes. The primary objective was noninferiority of dulaglutide 1.5 mg to glargine in the HbA_{1c} change from baseline at 52 weeks.

RESEARCH DESIGN AND METHODS

In this 78-week, open-label study, 810 patients were randomized to dulaglutide 1.5 mg, dulaglutide 0.75 mg, or glargine.

RESULTS

The baseline mean ± SD HbA_{1c} was 8.1 ± 1.0% (65.5 ± 10.8 mmol/mol). The least squares mean ± SE HbA_{1c} change from baseline to the primary end point was −1.08 ± 0.06% (−11.8 ± 0.7 mmol/mol) for dulaglutide 1.5 mg, −0.76 ± 0.06% (−8.3 ± 0.7 mmol/mol) for dulaglutide 0.75 mg, and −0.63 ± 0.06% (−6.9 ± 0.7 mmol/mol) for glargine, with an end point mean ± SD dose of 29 ± 26 units (0.33 ± 0.24 units/kg), and a fasting plasma glucose (mean ± SD) of 118 ± 23 mg/dL from self-monitored plasma glucose. Statistical criteria for superiority were met with dulaglutide 1.5 mg and for noninferiority with dulaglutide 0.75 mg. More patients on dulaglutide 1.5 mg achieved HbA_{1c} targets <7.0% (53 mmol/mol) versus glargine ($P < 0.001$). Body weight decreased with dulaglutide and increased with glargine. Total hypoglycemia rates were lower with dulaglutide; severe hypoglycemia was minimal. Increases in pancreatic enzymes were observed for dulaglutide. Incidence of nausea (15.4, 7.7, and 1.5%) and diarrhea (10.6, 9.2, and 5.7%) were more common with dulaglutide 1.5 mg and 0.75 mg than with glargine.

CONCLUSIONS

Once-weekly dulaglutide 1.5 mg, compared with daily insulin glargine without forced titration, demonstrated greater HbA_{1c} reduction and weight loss, with a higher incidence of gastrointestinal adverse events and a lower risk of hypoglycemia.

[1]*University of Bari Aldo Moro, Bari, Italy*
[2]*Evangelismos-Polyclinic, Athens General Hospital, Athens, Greece*
[3]*Chang Gung Memorial Hospital, Taoyuan Hsien, Taiwan*
[4]*Eli Lilly and Company, Indianapolis, IN*
[5]*Eli Lilly and Company, Neuilly-Sur-Seine Cedex, France*

Corresponding author: Valeria Pechtner, pechtner_valeria@lilly.com.

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Optimal glycemic control in type 2 diabetes is critical for the prevention of chronic complications of hyperglycemia. Given the progressive nature of the disease, characterized by the decline of β-cell function (1), initial nonpharmacological treatment is generally followed by progressive addition of oral antihyperglycemic medications (OAMs) and eventually, by adding basal insulin (2). Treatment with insulin glargine has been shown to be effective, particularly in controlling fasting hyperglycemia, but is not without adverse outcomes such as hypoglycemia and potential weight gain (3–5). This established approach to treatment optimization was justified when insulin was the only other available option. However, glucagon-like peptide-1 (GLP-1) receptor agonists have become available in recent years, and evidence exists that they represent a valid alternative to basal insulin, with similar or improved efficacy, weight loss, and lower risk of hypoglycemia when compared in head-to-head studies (6–10).

Dulaglutide is a long-acting human GLP-1 receptor agonist and consists of 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 linker (11). The GLP-1 analog portion of dulaglutide is 90% homologous to native human GLP-1(7-37) (12) and contains amino acid substitutions designed to optimize its clinical profile, including protection from dipeptidyl peptidase-4 inactivation, increased solubility, and reduction of immunogenicity (11,13). In addition, dulaglutide has a large size that slows absorption and reduces renal clearance (11,13). These engineering features result in a soluble formulation and a prolonged half-life of ~5 days, making it suitable for once-weekly subcutaneous administration (14). In phase 3 studies, dulaglutide demonstrated significant glycosylated hemoglobin A_{1c} (HbA_{1c}) reductions, with both fasting and postprandial glucose improvements, and weight loss (15–18). The objective of the AWARD-2 (Assessment of Weekly AdministRation of LY2189265 [dulaglutide] in Diabetes-2) study was to compare the efficacy and safety of once-weekly dulaglutide with once-daily insulin glargine in patients not optimally controlled on OAMs during a 78-week treatment period.

RESEARCH DESIGN AND METHODS

Eligible patients at screening were adults with an HbA_{1c} of ≥7.0% (≥53 mmol/mol) and ≤11.0% (≤97 mmol/mol), BMI ≥23 and ≤45 kg/m^2, and stable weight for ≥3 months, who were not optimally controlled with one, two, or three OAMs (of which one had to be metformin or a sulfonylurea) for at least 3 months. Patients were excluded from study participation if they had received chronic insulin therapy at any time in the past or had taken GLP-1 receptor agonists within 3 months of screening. Institutional review boards provided written approval of the protocol, and all patients provided written informed consent before any study-related activities. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines (19).

This open-label comparator (double-blind to dulaglutide dose), parallel-arm, randomized, multicenter trial consisted of three periods: a screening and lead-in period of ~10–12 weeks, a treatment period of 78 weeks, and a safety follow-up period of 4 weeks (Fig. 1*A*). During the first 2 to 3 weeks of the lead-in period, any other OAMs were discontinued, and metformin and glimepiride therapy were initiated and/or adjusted to maximally tolerated doses, but not higher than the maximum locally approved doses (minimum dose required: 1,500 mg/day for metformin and 4 mg/day for glimepiride). Patients' OAM doses were then stabilized for ~6–8 weeks before randomization, at which time a qualifying HbA_{1c} >6.5% (>48 mmol/mol) was required for ongoing eligibility.

Patients were randomized (1:1:1) to subcutaneously injected once-weekly dulaglutide 1.5 mg, dulaglutide 0.75 mg, or once-daily glargine according to a computer-generated random sequence using an interactive voice response system. Randomization was stratified by country and baseline HbA_{1c} (≤8.5%, >8.5% [≤69, >69 mmol/mol]). Dosing for patients randomized to glargine was started at 10 units once daily (20). Patients were instructed to adjust insulin doses according to a standard titration algorithm (Supplementary Table 1) with a target fasting plasma glucose (FPG) of <100 mg/dL (<5.6 mmol/L) and a recommended dose adjustment of 0 to 2 units for FPG of 100 to 119 mg/dL (5.6–6.7 mmol/L) (21). Glargine dose adjustments occurred every 3 to 4 days for the first 4 weeks of treatment, followed by once weekly through week 8. After week 8, patients were to continue to adjust glargine per the titration algorithm; the glargine dose was also reviewed and revised, as needed, at subsequent office visits. There was no central oversight of insulin titration. In all treatment groups, doses of glimepiride, followed by metformin, could be decreased or discontinued if the patient experienced recurrent hypoglycemia. Add-on glycemic 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 Supplementary Table 2.

The primary efficacy measure was the change in HbA_{1c} from baseline to 52 weeks. Secondary efficacy measures included changes in HbA_{1c} from baseline to 26 and 78 weeks, the percentage of patients achieving HbA_{1c} <7.0% (<53 mmol/mol) and ≤6.5% (≤48 mmol/mol), and changes in fasting serum glucose (FSG) determined by the central laboratory, 8-point self-monitored plasma glucose (SMPG) profiles, and glucagon.

Safety assessments included hypoglycemic episodes, adverse events (AEs), serious adverse events (SAEs), body weight, vital signs, electrocardiograms, laboratory parameters (e.g., serial calcitonin and pancreatic enzymes), and immunogenicity testing for dulaglutide anti-drug antibodies (ADAs). An independent Clinical Event Classification group adjudicated the following events for possible development of pancreatitis: investigator-reported pancreatitis (any form), AEs of severe or serious abdominal pain without known cause, and confirmed elevations of one or more pancreatic enzymes at least three times the upper limit of normal (ULN). Deaths and nonfatal cardiovascular AEs (e.g., myocardial infarction, coronary interventions, cerebrovascular events, hospitalization for unstable angina, and hospitalization for heart failure) were also adjudicated by a committee of physicians external to Eli Lilly and Company.

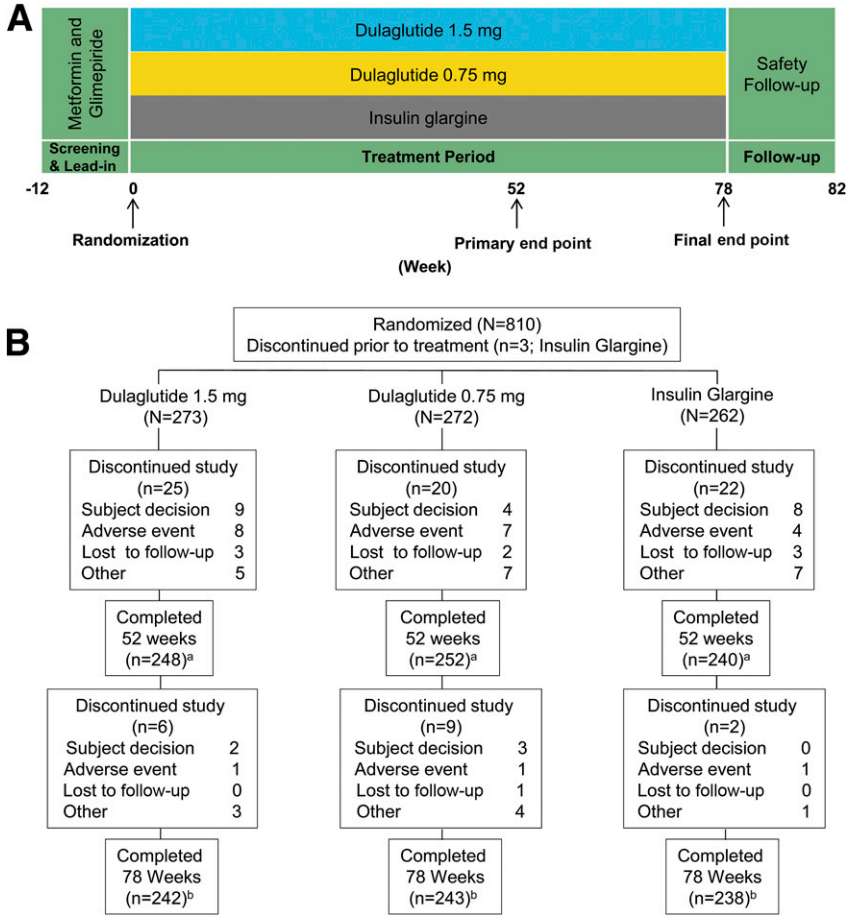

Figure 1—Study design (*A*) and patient disposition (*B*). [a]Rescue therapy was initiated for prespecified thresholds for severe, persistent hyperglycemia. The number of patients receiving rescue therapy was 11, 20, and 8 for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and glargine, respectively. [b]The number of patients receiving rescue therapy was 24, 34, and 16 for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and glargine, respectively.

Laboratory analyses were performed at a central laboratory (Quintiles Laboratories Europe, West Lothian, U.K.). Immunogenicity testing was performed by BioAgilytix (Durham, NC) and Millipore (St. Charles, MO).

On two separate days before prespecified visits, 8-point SMPG profiles were performed before and after meals, bedtime, and at 0300 h or 5 h after bedtime. Total hypoglycemia was defined as a plasma glucose level of ≤70 mg/dL (≤3.9 mmol/L) and/or signs and/or symptoms associated with hypoglycemia. Documented symptomatic hypoglycemia was defined as any time a patient experienced symptoms and/or signs associated with hypoglycemia and had a plasma glucose level of ≤70 mg/dL (≤3.9 mmol/L). Severe hypoglycemia was defined as an episode that required assistance from another person to actively administer therapy, as determined by the investigator (22).

Statistical Analyses

The study was designed with 90% power to show noninferiority of dulaglutide 1.5 mg versus glargine for change from baseline in HbA_{1c} at the 52-week primary end point with a margin of 0.4%, a SD of 1.3%, and a one-sided α of 0.025, assuming no true difference between treatments. This corresponded to 279 patients per arm, with an assumed dropout rate of 20%. If noninferiority was achieved, tree-gatekeeping (23) was used to control the type 1 error rate at 0.025 while assessing the superiority of dulaglutide 1.5 mg versus glargine and the noninferiority or superiority of dulaglutide 0.75 mg versus glargine for the change from baseline in HbA_{1c} at 52 weeks. *P* values were adjusted so that each could be compared with 0.025 to assess significance while accounting for multiplicity adjustments (24).

Efficacy and safety analyses were based on the intent-to-treat (ITT) population consisting of all randomized patients who received at least one dose of study treatment. For the assessment of efficacy, weight, and hypoglycemia events, only data obtained before initiation of rescue therapy were used.

The changes from baseline in HbA_{1c} and body weight at 52 and 78 weeks were analyzed using ANCOVA with factors for treatment, country, and the baseline value as a covariate. The last observation was carried forward (LOCF) in the case of missing data. Methods for other continuous secondary measures and HbA_{1c} and body weight over time included a mixed-effects model, repeated-measures analysis with factors for treatment, country, visit, 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 using a logistic regression model with treatment, country, and baseline HbA_{1c} as covariates. The percentage of patients experiencing AEs or hypoglycemia was analyzed using a χ^2 test, unless there were too few events to meet the assumptions of the analysis, in which case a Fisher exact test was conducted. The hypoglycemia rate was analyzed with a negative binomial model. For quantitative analysis of pancreatic enzymes, overall comparison by ANOVA on rank-transformed values was performed; if the overall comparison was significant, then a pairwise comparison with the Wilcoxon rank sum test was presented. The χ^2 test was used to analyze the percentage of patients with elevations of pancreatic enzymes. The two-sided significance level was 0.05 for secondary end points and 0.10 for interactions.

RESULTS

The study randomized 810 patients. Three patients in the glargine group discontinued before receiving the first dose and were subsequently excluded from the ITT population. A total of 740 patients completed through the 52-week study period, and 723 patients completed the study at 78 weeks (Fig. 1*B*). Overall demographic and baseline

characteristics were comparable between groups (Table 1). The number of patients who discontinued the study was similar across groups; the most common reason was patient decision, followed by AEs (Fig. 1*B*). The number of patients receiving rescue therapy was 24, 34, and 16 for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and glargine, respectively.

Baseline glimepiride and metformin doses are included in Table 1. At 52 weeks, the mean ± SD dose of glimepiride was 5.4 ± 2.3, 5.6 ± 2.2, and 5.4 ± 2.3 mg/day for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and glargine, respectively; 85% of patients overall were taking at least 4 mg/day. At 52 weeks, the mean ± SD daily metformin dose was 2,332 ± 553, 2,397 ± 471, and 2,390 ± 497 mg/day, respectively, for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and glargine; 98% of patients overall were taking at least 1,500 mg/day. At 52 weeks, ~30% of patients had decreased or discontinued their dose of glimepiride, and ~7% had decreased or discontinued their dose of metformin; these changes were balanced across treatment groups. At 52 weeks, the daily dose of glargine (mean ± SD) was (LOCF) 29 ± 26 units (0.33 ± 0.24 units/kg). In the glargine group, 24% of patients achieved the FPG target of <100 mg/dL (<5.6 mmol/L), and 58% of glargine-treated patients had an FPG of <120 mg/dL (<6.7 mmol/L).

Efficacy

The LS mean ± SE HbA_{1c} change from baseline to the 52-week primary end point was −1.08 ± 0.06% (−11.8 ± 0.7 mmol/mol), −0.76 ± 0.06% (−8.3 ± 0.7 mmol/mol), and −0.63 ± 0.06% (−6.9 ± 0.7 mmol/mol) for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and glargine, respectively (Fig. 2*A* and Supplementary Table 3). Statistical criteria for superiority was met with dulaglutide 1.5 mg, LS mean difference (nominal 95% CI) of −0.45% (−0.60 to −0.29) (−4.92 [−6.56 to −3.17] mmol/mol) (adjusted one-sided $P < 0.001$). Statistical criteria for noninferiority were met for dulaglutide 0.75 mg, −0.13% (−0.29 to 0.02) (−1.42 [–3.17 to 0.22] mmol/mol) (adjusted one-sided $P < 0.001$). At 52 weeks, the LS mean ± SE HbA_{1c} was 7.05 ± 0.06% (53.6 ± 0.7 mmol/mol), 7.37 ± 0.06% (57.1 ± 0.7 mmol/mol), and 7.50 ± 0.06% (58.5 ± 0.7 mmol/mol) for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and glargine, respectively.

The LS mean ± SE HbA_{1c} change from baseline at 78 weeks was −0.90 ± 0.07% (−9.8 ± 0.8 mmol/mol), −0.62 ± 0.07% (−6.8 ± 0.8 mmol/mol), and −0.59 ± 0.07% (−6.5 ± 0.8 mmol/mol) for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and glargine, respectively (Fig. 2*A*). Statistical criteria for superiority were met with dulaglutide 1.5 mg, LS mean difference (nominal 95% CI) of −0.31% (−0.50 to −0.13) (−3.39 [–5.46 to −1.42] mmol/mol) (adjusted one-sided $P < 0.001$). Statistical criteria for noninferiority were met for dulaglutide 0.75 mg, −0.03% (−0.21 to 0.15) (−0.33 [–2.3 to 1.64] mmol/mol) (adjusted one-sided $P < 0.001$). Figure 2*B* depicts HbA_{1c} over time up to 78 weeks.

At 52 weeks, a greater percentage of patients on dulaglutide 1.5 mg (53.2%) achieved an HbA_{1c} target of <7.0% (<53 mmol/mol) compared with the glargine group (30.9%; $P < 0.001$) (Fig. 2*C*). There was no significant difference in percentages of patients who achieved the HbA_{1c} target of <7.0% (<53 mmol/mol) for dulaglutide 0.75 mg (37.1%) compared with glargine. Greater percentages of patients on dulaglutide 1.5 mg (27.0%) and dulaglutide 0.75 mg (22.5%) achieved an HbA_{1c} target ≤6.5% (≤48 mmol/mol) than with glargine (13.5%) ($P < 0.001$ and $P = 0.004$, respectively). At 78 weeks, percentages of patients attaining HbA_{1c} targets were generally maintained, except for the percentage of patients with an HbA_{1c} of ≤6.5% (≤48 mmol/mol), which was similar for dulaglutide 0.75 mg and glargine.

The reduction in mean FSG (central laboratory value) was maximal at 2 weeks for both dulaglutide doses (Fig. 2*D*). By 52 weeks, the LS mean ± SE change from baseline in FSG was −27 ± 3, −16 ± 3, and −32 ± 3 mg/dL for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and glargine, respectively, with a greater decrease for glargine than dulaglutide 0.75 mg ($P < 0.001$). The LS mean ± SE FSG at week 52 was 135 ± 2.5, 146 ± 2.6, and 130 ± 2.6 mg/dL for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and glargine, respectively. At 78 weeks, treatment with glargine resulted

Table 1—Baseline characteristics and demographics of patients

Variable	Dulaglutide 1.5 mg *N* = 273	Dulaglutide 0.75 mg *N* = 272	Glargine *N* = 262
Sex, *n* (%)			
Men	144 (53)	136 (50)	134 (51)
Women	129 (47)	136 (50)	128 (49)
Age (years)	56 ± 10	57 ± 9	57 ± 9
Race, *n* (%)			
American Indian or Alaska Native	29 (11)	31 (11)	29 (11)
Asian	48 (18)	46 (17)	43 (16)
Black or African American	1 (<1)	1 (<1)	2 (1)
Multiple	2 (1)	1 (<1)	4 (2)
White	193 (71)	193 (71)	184 (70)
Ethnicity, *n* (%)			
Hispanic	98 (36)	96 (35)	97 (37)
Non-Hispanic	175 (64)	176 (65)	165 (63)
Weight (kg)	85 ± 18	86 ± 18	88 ± 20
BMI (kg/m^2)	31 ± 5	32 ± 5	32 ± 6
Diabetes duration (years)	9 ± 6	9 ± 6	9 ± 6
HbA_{1c} (%)	8.2 ± 1.0	8.1 ± 1.0	8.1 ± 1.0
HbA_{1c} (mmol/mol)	65.9 ± 11.3	65.4 ± 10.7	65.0 ± 10.4
Fasting serum glucose (mg/dL)	165 ± 49	161 ± 49	163 ± 48
Glimepiride dose (mg/day)	6.3 ± 1.7	6.3 ± 1.6	6.2 ± 1.6
Metformin dose (mg/day)	2,379 ± 480	2,412 ± 495	2,419 ± 475
Prestudy treatment (%)*			
1 OAM	16.5	15.4	16.2
2 OAMs	67.8	65.4	66.4
>2 OAMs	15.8	19.1	17.4

Data are mean ± SD or *n* (%) unless otherwise indicated. *At screening.

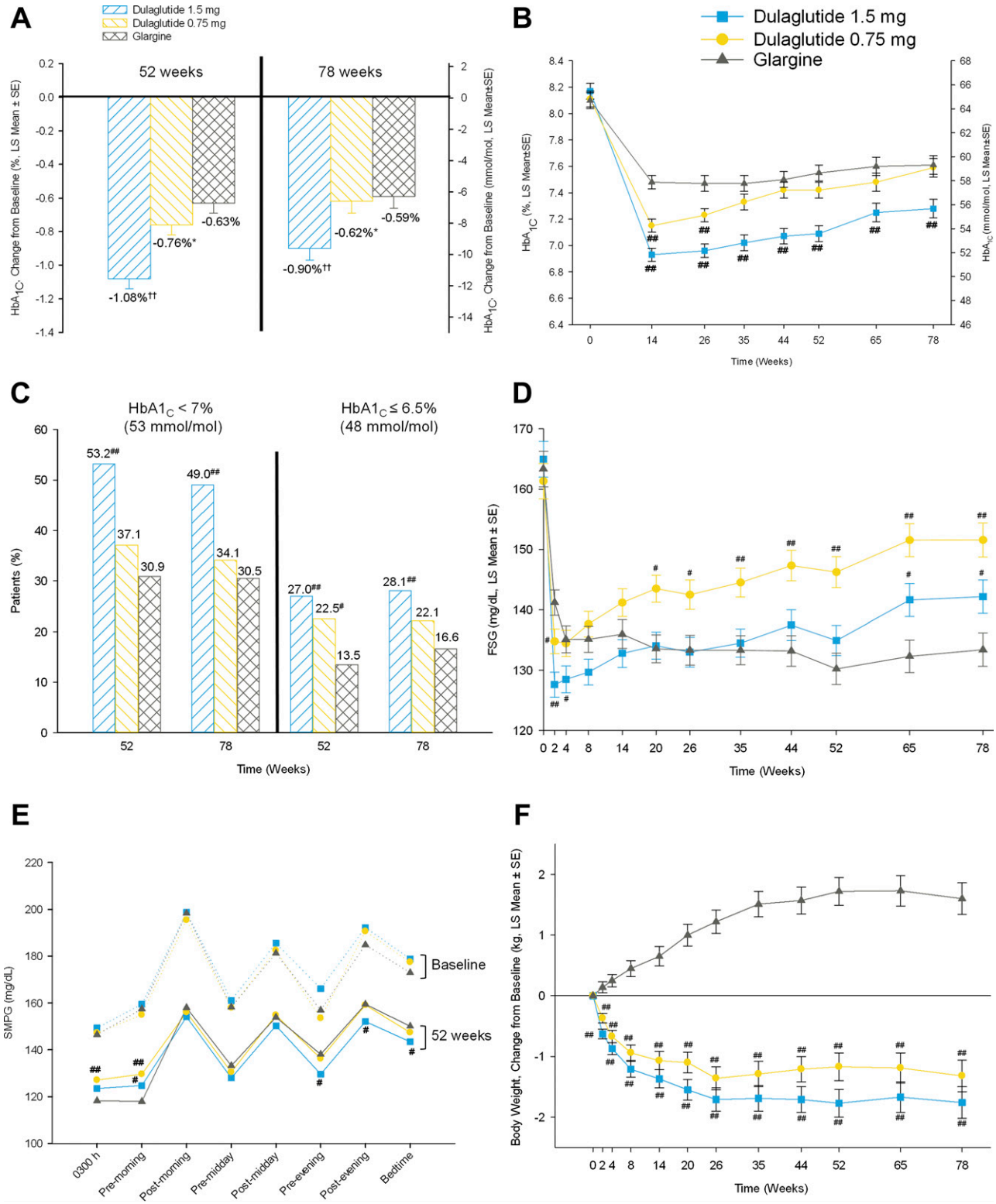

Figure 2—Efficacy and safety measures through the treatment period. *A*: Change in HbA_{1c} from baseline at 52 and 78 weeks, (ANCOVA) LOCF. *B*: HbA_{1c} over time (mixed-effects model repeated measures [MMRM]). *C*: Percentage of patients achieving HbA_{1c} targets (logistic regression). *D*: FSG over time (MMRM). *E*: Baseline (dashed lines) and 52-week (solid lines) 8-point SMPG profiles (MMRM). *F*: Change in body weight over time (MMRM). Data presented are LS mean ± SE. ††$P < 0.001$, superiority vs. glargine; *$P < 0.001$, noninferiority vs. glargine; #$P < 0.05$ vs. glargine; ##$P < 0.001$ vs. glargine.

in a greater decrease in FSG than both dulaglutide groups ($P < 0.05$ for dulaglutide 1.5 mg and $P < 0.001$ for dulaglutide 0.75 mg).

At 52 weeks, the FPG from 8-point SMPG profiles decreased more with glargine than with dulaglutide 1.5 mg and dulaglutide 0.75 mg (Fig. 2*E* and Supplementary Table 4). The decrease from baseline for the 2-h postprandial plasma glucose (PPG) was similar after the morning and midday meals and

greater after the evening meal with dulaglutide 1.5 mg than with glargine, resulting in a greater decrease from baseline for overall daily mean PPG for dulaglutide 1.5 mg. Generally, similar 8-point SMPG profile results were observed at 78 weeks (Supplementary Fig. 1 and Supplementary Table 4).

Over time, patients in dulaglutide treatment groups exhibited body weight loss, while those in the glargine group gained weight (Fig. 2*F*). At week 52, the LS mean ± SE changes from baseline in body weight for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and glargine were −1.87 ± 0.24, −1.33 ± 0.24, and 1.44 ± 0.24 kg, respectively; the differences between the dulaglutide treatment arms and glargine were significant ($P < 0.001$ for both dulaglutide doses). At 78 weeks, the LS mean changes were maintained.

There were no between-group differences in glucagon or lipid parameters, other than a small decrease in LDL observed with dulaglutide 0.75 mg compared with glargine at 52 weeks (Supplementary Table 5).

Safety

The overall incidence of SAEs was similar across the three treatment groups (Table 2). Three deaths occurred during the study (dulaglutide 0.75 mg: 1 of heart failure; glargine: 1 of respiratory failure and 1 of sudden death). The proportion of patients who reported at least one AE during the 78-week treatment period was similar between groups. The discontinuation rates due to AEs were similar across treatment arms: 3.3% dulaglutide 1.5 mg, 2.9% dulaglutide 0.75 mg, and 1.9% glargine. The three most frequently reported AEs for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and glargine, respectively, were diarrhea (10.6, 9.2, and 5.7%), nausea (15.4, 7.7, and 1.5%), and nasopharyngitis (5.5, 4.4, and 8.8%) (Table 2). Nausea was more frequent in both dulaglutide arms versus glargine ($P < 0.001$ for both comparisons), and ≥96% of the diarrhea and nausea events were mild to moderate in severity. The prevalence of nausea was highest at the first postbaseline visit (week 2) and then declined thereafter (Supplementary Fig. 2). Three cases of pancreatitis, two in dulaglutide 1.5 mg and one in dulaglutide 0.75 mg, were confirmed by adjudication, two acute and one chronic. One case of acute pancreatitis was reported 1 day after starting dulaglutide 0.75 mg in an asymptomatic patient; the workup was initiated based on elevated pancreatic enzymes from a blood sample drawn before the patient had received the first dose of dulaglutide, and the patient subsequently had positive imaging. The other patient with acute pancreatitis was diagnosed 302 days after initiation of dulaglutide 1.5 mg based on symptoms, elevated enzymes, and positive imaging. The patient with chronic pancreatitis was diagnosed 107 days after starting dulaglutide 1.5 mg based on elevated enzymes and positive imaging.

The incidence of total hypoglycemia up to 52 weeks was lower for dulaglutide 1.5 mg and dulaglutide 0.75 mg compared with glargine: 55.3, 54.4, and 69.1%, respectively ($P = 0.001$ for dulaglutide 1.5 mg and $P < 0.001$ dulaglutide 0.75 mg) (Supplementary Table 6). Mean rates of total hypoglycemia were lower compared with glargine for both dulaglutide groups: 5.2, 4.8, and 7.9 events/patient/year for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and glargine, respectively ($P = 0.002$ for dulaglutide 1.5 mg and $P < 0.001$ dulaglutide 0.75 mg) (Supplementary Table 6). Nocturnal hypoglycemia was more frequent with glargine (2.1 events/patient/year) than with dulaglutide 1.5 mg and dulaglutide 0.75 mg (0.9 and 0.7 events/patient/year; $P < 0.001$ for both comparisons). Results at 78 weeks were generally similar to those observed at 52 weeks (Supplementary Table 7). During the 78-week treatment period, four patients experienced severe hypoglycemia: two in the glargine group (both on concomitant glimepiride) and two in the dulaglutide 1.5 mg group (one elderly patient who had previously discontinued glimepiride and presented with blood glucose of 45 mg/dL and loss of consciousness was treated in the emergency department with intravenous glucose, and the other patient while taking glimepiride).

No significant differences between dulaglutide and glargine were observed for changes in systolic and diastolic blood pressure (Table 2). The mean heart rate increased in both dulaglutide groups and decreased in the glargine group. Small increases in median pancreatic enzymes that remained within the normal range were observed for dulaglutide compared with glargine (Supplementary Table 8), as well as increased numbers of patients with transient elevations of lipase of more than three times ULN (Table 2). Calcitonin levels remained stable throughout the study.

Treatment-emergent ADAs developed in 15 dulaglutide-treated patients (2.8%) at least once after baseline; dulaglutide-neutralizing antibodies developed in 5, but no native sequence GLP-1 neutralizing–antibodies developed. A review of individual HbA_{1c} values of these patients did not show any unusual pattern. Four dulaglutide-treated patients (2 patients in each dulaglutide group) experienced injection-site reactions; none were serious or resulted in discontinuation of the study drug. No patients reported hypersensitivity reactions.

CONCLUSIONS

In this 78-week open-label study, once-weekly dulaglutide 1.5 mg was more effective in reducing HbA_{1c} than glargine in patients with type 2 diabetes treated with maximally tolerated doses of metformin and glimepiride and was associated with body weight loss and a lower risk of hypoglycemia. Notably, in the current study, the glargine dose was not titrated to fasting euglycemia in most patients.

An optimal balance between benefit in glycemic control and risk of hypoglycemia is of critical importance when considering options for advancing to injectable therapy in patients with type 2 diabetes uncontrolled on OAMs. With use of basal insulin, this balance can be difficult to achieve. Other trials of GLP-1 receptor agonists assessing efficacy compared with glargine (6–10) have demonstrated statistically similar or greater HbA_{1c} lowering versus glargine; again, with glargine therapy consistently resulting in a higher risk of hypoglycemia and weight gain (6–10). This comparative risk-to-benefit profile has contributed to the clinical interest in the GLP-1 receptor agonist class as an alternative option for patients progressing to therapy beyond OAMs.

In AWARD-2, dulaglutide demonstrated expected glycemic efficacy and weight loss, consistent with published results from AWARD studies (15–18). Along with a significant effect on HbA_{1c}, the maximum decrease in mean fasting glucose with dulaglutide occurred

Table 2—Safety assessments

Variable	52 weeks*			78 weeks*†		
	Dulaglutide		Glargine	Dulaglutide		Glargine
	1.5 mg *N* = 273	0.75 mg *N* = 272	*N* = 262	1.5 mg *N* = 273	0.75 mg *N* = 272	*N* = 262
Death, *n* (%)	0 (0)	0 (0)	2 (0.8)	0 (0.0)	1 (0.4)	2 (0.8)
Serious adverse events, *n* (%)	24 (8.8)	23 (8.5)	28 (10.7)	32 (11.7)	28 (10.3)	32 (12.2)
TEAEs (patients with ≥1 event), *n* (%)	189 (69.2)	175 (64.3)	175 (66.8)	201 (73.6)	188 (69.1)	192 (73.3)
TEAEs (≥5% patients), *n* (%)						
Gastrointestinal events						
Diarrhea	29 (10.6)#	23 (8.5)#	10 (3.8)	29 (10.6)	25 (9.2)	15 (5.7)
Nausea	39 (14.3)##	18 (6.6)#	4 (1.5)	42 (15.4)##	21 (7.7)##	4 (1.5)
Dyspepsia	18 (6.6)#	9 (3.3)	6 (2.3)	19 (7.0)#	9 (3.3)	6 (2.3)
Vomiting	17 (6.2)#	9 (3.3)	3 (1.1)	18 (6.6)#	10 (3.7)	3 (1.1)
Abdominal pain upper	13 (4.8)#	8 (2.9)	2 (0.8)	14 (5.1)#	9 (3.3)#	2 (0.8)
Infections and infestations						
Bronchitis	5 (1.8)	4 (1.5)	9 (3.4)	9 (3.3)	6 (2.2)	14 (5.3)
Influenza	11 (4.0)	13 (4.8)	10 (3.8)	12 (4.4)	13 (4.8)	13 (5.0)
Nasopharyngitis	13 (4.8)	7 (2.6)	17 (6.5)	15 (5.5)	12 (4.4)	23 (8.8)
Upper respiratory tract infection	14 (5.1)	7 (2.6)	14 (5.3)	15 (5.5)	10 (3.7)	17 (6.5)
Urinary tract infection	8 (2.9)	12 (4.4)	11 (4.2)	11 (4.0)	16 (5.9)	15 (5.7)
Nervous system disorders						
Headache	21 (7.7)	7 (2.6)	10 (3.8)	22 (8.1)	9 (3.3)	13 (5.0)
Discontinuation due to an AE, *n* (%)	8 (2.9)	7 (2.6)	4 (1.5)	9 (3.3)	8 (2.9)	5 (1.9)
Pancreatic enzymes, mean ± SD (units/L)						
Lipase (baseline)	56.6 ± 64.7	47.6 ± 47.1	46.5 ± 32.9	56.6 ± 64.7	47.6 ± 47.1	46.5 ± 32.9
Lipase Δ	4.7 ± 63.8	4.3 ± 54.4	2.2 ± 81.4	3.9 ± 66.2	9.3 ± 61.6	−4.0 ± 33.1
Total amylase (baseline)	68.6 ± 36.4	63.0 ± 29.5	62.1 ± 29.3	68.6 ± 36.4	63.0 ± 29.5	62.1 ± 29.3
Total amylase Δ	5.4 ± 31.2	4.5 ± 21.4	1.6 ± 28.8	6.4 ± 32.3	5.2 ± 21.8	0.76 ± 25.8
Pancreatic amylase (baseline)	34.0 ± 27.4	29.4 ± 20.6	29.1 ± 19.5	34.0 ± 27.4	29.4 ± 20.6	29.1 ± 19.5
Pancreatic amylase Δ	3.6 ± 25.6	2.9 ± 18.8	1.4 ± 26.2	3.9 ± 30.3	3.8 ± 18.1	−0.38 ± 19.4
Patients with at least 1 TE abnormality, *n* (%)‡						
Lipase	97 (35.5)##	76 (27.9)#	46 (17.6)	102 (37.4)##	85 (31.3)#	50 (19.1)
Total amylase	43 (15.8)#	37 (13.6)	22 (8.4)	43 (15.8)#	42 (15.4)#	24 (9.2)
Pancreatic amylase	42 (15.4)	51 (18.8)#	29 (11.1)	44 (16.1)	61 (22.4)#	34 (13.0)
Pancreatic enzymes, *n* (%) patients with >3× ULN§						
Lipase (baseline)	11 (4.0)	4 (1.5)	8 (3.1)	11 (4.0)	4 (1.5)	8 (3.1)
Lipase	38 (14.1)##	20 (7.5)	14 (5.4)	45 (16.7)##	23 (8.6)	14 (5.4)
Total amylase (baseline)	0	0	0	0	0	0
Total amylase	4 (1.5)	1 (0.4)	1 (0.4)	4 (1.5)	1 (0.4)	1 (0.4)
Pancreatic amylase (baseline)	4 (1.5)	2 (0.7)	1 (0.4)	4 (1.5)	2 (0.7)	1 (0.4)
Pancreatic amylase	12 (4.5)	7 (2.6)	3 (1.2)	14 (5.2)	10 (3.7)	4 (1.6)
Vital signs‖						
Blood pressure (mmHg)						
Systolic (baseline)	132 ± 16	131 ± 14	130 ± 16	132 ± 16	131 ± 14	130 ± 16
Systolic Δ	0.17 ± 0.81	0.09 ± 0.80	0.51 ± 0.83	−0.70 ± 0.85	−0.59 ± 0.85	0.51 ± 0.87
Diastolic (baseline)	79 ± 9	79 ± 9	78 ± 9	79 ± 9	79 ± 9	78 ± 9
Diastolic Δ	−0.26 ± 0.48	−0.19 ± 0.47	−0.93 ± 0.49	−0.44 ± 0.52	−0.36 ± 0.52	−1.04 ± 0.53
Heart rate (bpm) (baseline)	76.14 ± 9.74	76.99 ± 10.05	76.72 ± 9.24	76.14 ± 9.74	76.99 ± 10.05	76.72 ± 9.24
Heart rate Δ	1.29 ± 0.50#	0.51 ± 0.49	−0.52 ± 0.51	1.31 ± 0.50#	0.61 ± 0.50#	−0.91 ± 0.51

Δ, change from baseline at 52 or 78 weeks; TEAE, treatment-emergent adverse event. *For all adverse events, an overall *P* value was calculated. Pairwise *P* values were reported only to compare with glargine and only when the overall $P \leq 0.05$ and both groups had events. †The 78-week count data are cumulative and include data through 52 weeks. ‡Patients with at least 1 treatment-emergent abnormality during the time period assessed. §Patients with at least 1 value >3× ULN during the time period assessed. ‖Baseline data are presented as mean ± SD; change from baseline data are presented as LS mean ± SE. #$P < 0.05$ vs. glargine. ##$P < 0.001$ vs. glargine.

within 2 weeks of treatment initiation. This confirms the known pharmacokinetic profile and rapidity of action with dulaglutide and, in comparison with glargine, obviates the need for daily dose adjustment based on glucose monitoring. As expected, based on the use of a targeted treatment algorithm, self-measured fasting glucose decreased more with insulin glargine than with either dose of dulaglutide. Although of note, dulaglutide 1.5 mg demonstrated a greater effect on glucose control in the evening, with lower predinner, postdinner, and bedtime glucose levels. Given the difference observed in HbA_{1c} changes, one could speculate that dulaglutide treatment led to a relative improvement in interprandial glucose levels at other times throughout the day, although the study did not thoroughly assess this. Because dulaglutide

demonstrates effects on both fasting glucose and PPG, future areas of investigation could include comparison with other insulin regimens that affect both fasting glucose and PPG.

The main limitation of this study is the mean total daily dose of 29 units achieved with glargine titration at the primary end point. Without central committee monitoring of insulin adjustments, strict enforcement of the insulin titration algorithm was not accomplished. It is possible that a more stringent titration of basal insulin resulting in a lower mean FPG would have resulted in a greater decrease of HbA_{1c} than that observed in the current study.

The safety profile of dulaglutide in AWARD-2 is consistent with prior dulaglutide data and with data from other compounds in the class (6,8,9,25). The most frequently reported AEs for dulaglutide were gastrointestinal (e.g., diarrhea, nausea). As previously reported for GLP-1 receptor agonist therapy (15–18,26–28), median levels of pancreatic enzymes increased with dulaglutide, as did the incidence of patients with transient elevations of lipase that were above three times the ULN (incidence over 78 weeks of 17%, 9%, and 5% for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and glargine, respectively) during the course of the treatment. These changes were not predictive of pancreatitis, and their clinical relevance is unknown. Adjudicated pancreatitis was reported in three dulaglutide-treated patients in this study. These three cases are included in the total count of five adjudicated pancreatitis events (1.4 cases/1,000 patient-years) associated with dulaglutide in the phase 2 and 3 clinical development program compared with one confirmed case in nonincretin comparators (0.88 cases/1,000 patient-years) (12). Dulaglutide exhibited low immunogenicity, with dulaglutide ADAs developing in few patients (2.8%). Also, few patients experienced injection-site reactions, and no AEs were associated with systemic hypersensitivity. Heart rate changes observed were consistent with previous reports of dulaglutide (15–18,29) and the GLP-1 receptor agonist class (15,18,27,30). To date, clinical consequences have not been associated with these modest increases; cardiovascular safety will be further assessed in the ongoing dulaglutide cardiovascular outcomes study Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND; NCT01394952).

In this study in patients with type 2 diabetes receiving concomitant maximally tolerated doses of metformin and glimepiride, treatment with once-weekly dulaglutide 1.5 mg for up to 78 weeks resulted in clinically meaningful improvement in glycemic control associated with body weight loss, a higher incidence of gastrointestinal AEs, and a lower risk of hypoglycemia compared with insulin glargine without forced titration.

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