Efficacy and Safety of Dulaglutide Monotherapy Versus Metformin in Type 2 Diabetes in a Randomized Controlled Trial (AWARD-3)

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OBJECTIVE

Compare the efficacy and safety of monotherapy with dulaglutide, a once-weekly GLP-1 receptor agonist, to metformin-treated patients with type 2 diabetes. The primary objective compared dulaglutide 1.5 mg and metformin on change from baseline glycosylated hemoglobin A_{1c} (HbA_{1c}) at 26 weeks.

RESEARCH DESIGN AND METHODS

This 52-week double-blind study randomized patients to subcutaneous dulaglutide 1.5 mg, dulaglutide 0.75 mg, or metformin. Patients (*N* = 807) had HbA_{1c} ≥6.5% (≥48 mmol/mol) and ≤9.5% (≤80 mmol/mol) with diet and exercise alone or low-dose oral antihyperglycemic medication (OAM) monotherapy; OAMs were discontinued at beginning of lead-in period.

RESULTS

At 26 weeks, changes from baseline HbA_{1c} (least squares [LS] mean ± SE) were: dulaglutide 1.5 mg, −0.78 ± 0.06% (−8.5 ± 0.70 mmol/mol); dulaglutide 0.75 mg, −0.71 ± 0.06% (−7.8 ± 0.70 mmol/mol); and metformin, −0.56 ± 0.06% (−6.1 ± 0.70 mmol/mol). Dulaglutide 1.5 and 0.75 mg were superior to metformin (LS mean difference): −0.22% (−2.4 mmol/mol) and −0.15% (−1.6 mmol/mol) (one-sided *P* < 0.025, both comparisons), respectively. Greater percentages reached HbA_{1c} targets <7.0% (<53 mmol/mol) and ≤6.5% (≤48 mmol/mol) with dulaglutide 1.5 and 0.75 mg compared with metformin (*P* < 0.05, all comparisons). No severe hypoglycemia was reported. Compared with metformin, decrease in weight was similar with dulaglutide 1.5 mg and smaller with dulaglutide 0.75 mg. Over 52 weeks, nausea, diarrhea, and vomiting were the most common adverse events; incidences were similar between dulaglutide and metformin.

CONCLUSIONS

Dulaglutide improves glycemic control and is well tolerated as monotherapy in patients with early stage type 2 diabetes.

Muscle and liver insulin resistance and β-cell failure represent the core pathophysiologic defects in type 2 diabetes. In addition, there is increasing evidence that the gastrointestinal (GI) tract plays an essential role in the development of carbohydrate intolerance of type 2 diabetes (1). The incretin concept suggests that ingested glucose results in a considerably larger and more sustained insulin secretion compared with glucose administered intravenously due to the release of two intestinal-derived

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hormones that stimulate insulin release: glucose-dependent insulinotropic polypeptide and GLP-1 (2,3). Additionally, GLP-1 has been shown to inhibit glucagon secretion (4), slow gastric emptying (5), and cause reduction of food intake (6,7). Endogenous GLP-1 is rapidly inactivated by the protease dipeptidyl peptidase-4. To overcome this limitation of native GLP-1, GLP-1 receptor agonists with prolonged time-action profiles have been developed for use in treatment of patients with type 2 diabetes.

Dulaglutide is a long-acting human GLP-1 receptor agonist (8). The molecule consists of two identical, disulfide-linked chains, each containing an N-terminal GLP-1 analog sequence covalently linked to a modified human immunoglobulin G4 Fc heavy chain by a small peptide linker (9). In contrast to native GLP-1, dulaglutide is resistant to degradation by dipeptidyl peptidase-4 and has a large size that slows absorption and reduces renal clearance. These engineering 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. In phase 2 studies, dulaglutide demonstrated significant dose-dependent improvements in glycemic control and body weight and a low rate of hypoglycemia (10,11). The most frequent side effects of dulaglutide in these studies were GI related, as observed with other GLP-1 receptor agonists (10–12).

The current standards of care for medical management of hyperglycemia in type 2 diabetes recommends metformin monotherapy as a first-line therapy due to its strong glucose-lowering effect without weight gain and low hypoglycemia risk (13). Similar to GLP-1 receptor agonists, the most common side effects of metformin are GI in nature, with up to 10% of treated patients discontinuing this agent due to GI intolerance (14). Since GLP-1 receptor agonists have beneficial effects on multiple pathophysiological abnormalities of type 2 diabetes, it is of significant clinical interest to assess their therapeutic potential in various stages of the disease. The Assessment of Weekly AdministRation of LY2189265 [dulaglutide] in Diabetes-3 (AWARD-3) study was designed to evaluate the efficacy and safety of monotherapy with once-weekly dulaglutide compared with daily metformin in patients with early stage type 2 diabetes over a period of 52 weeks.

RESEARCH DESIGN AND METHODS

Patients ≥18 years of age were eligible to participate if they had type 2 diabetes for a duration of ≥3 months and ≤5 years, glycosylated hemoglobin A_{1c} (HbA_{1c}) ≥6.5% (≥48 mmol/mol) and ≤9.5% (≤ 80 mmol/mol), were on diet and exercise alone, or on one oral antihyperglycemic medication (OAM) for ≥3 months prior to screening. Individuals who were receiving an OAM were only eligible if they were taking ≤50% of the approved maximum daily dose per respective labels in participating countries. Patients were excluded from the study if they had been taking thiazolidinediones or GLP-1 receptor agonists during the 3 months prior to screening or had ever received chronic insulin therapy. Institutional review boards provided written approval of the protocol, and 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 Harmonization guideline on good clinical practices (15). Data were collected from study participants between 24 May 2010 and 19 June 2012.

This 52-week, randomized, parallel-arm, double-blind, double-dummy (both injectable and oral placebo), noninferiority study consisted of three periods: lead-in (~2 weeks), treatment (52 weeks), and safety follow-up (4 weeks) (Fig. 1*A*). During the lead-in period, patients discontinued any previous OAM for a 2-week washout. Randomization occurred, stratified by country and prior OAM use, according to a computer-generated random sequence using an Interactive Voice Response System to one of three arms (1:1:1): once-weekly, subcutaneously injected dulaglutide 1.5 mg, dulaglutide 0.75 mg, or daily metformin. Metformin was progressively titrated up to 2,000 mg/day during the first 4 weeks of treatment or at least 1,500 mg/day depending upon tolerability. Standard dietary and physical activity counseling was provided. An add-on rescue therapy was allowed for patients who met prespecified criteria for severe, persistent hyperglycemia. A detailed description of protocol-specified thresholds for intervention is provided in the Supplementary Material.

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

Safety assessments at 26 and 52 weeks included adverse events, hypoglycemic episodes, vital signs, electrocardiograms, laboratory parameters (i.e., serial calcitonin and pancreatic enzymes), and dulaglutide antidrug antibody testing. GI side effects were further assessed using the Gastrointestinal Clinical Symptoms Index (GCSI), a validated questionnaire for gastroparesis symptoms that includes three subscales (postprandial fullness/early satiety, nausea/vomiting, and bloating) and an overall score (16). For each item, 0 represented "none" and 5 indicated "very severe." The following events were adjudicated by an independent Clinical Events Classification Group to assess for possible development of pancreatitis: investigator-reported pancreatitis (any form), serious or severe abdominal pain without known cause, and asymptomatic confirmed elevations (≥3 times upper limit of normal [ULN]) in pancreatic enzymes. Laboratory analyses were performed at a central laboratory (Quintiles Laboratories). HbA_{1c} was assayed by high-performance liquid chromatography. Immunogenicity testing was performed by BioAgilytix Labs (Durham, NC) and Millipore (Billerica, MA). Commercially available glucose meters and test strips were provided. On two separate dates in the week prior to each treatment period visit, eight-point SMPG profiles were performed (before and after meals, bedtime, and 0300 h or 5 h after bedtime). Total hypoglycemia was defined as plasma glucose ≤70 mg/dL (≤3.9 mmol/L) and/or symptoms and/or signs attributable to

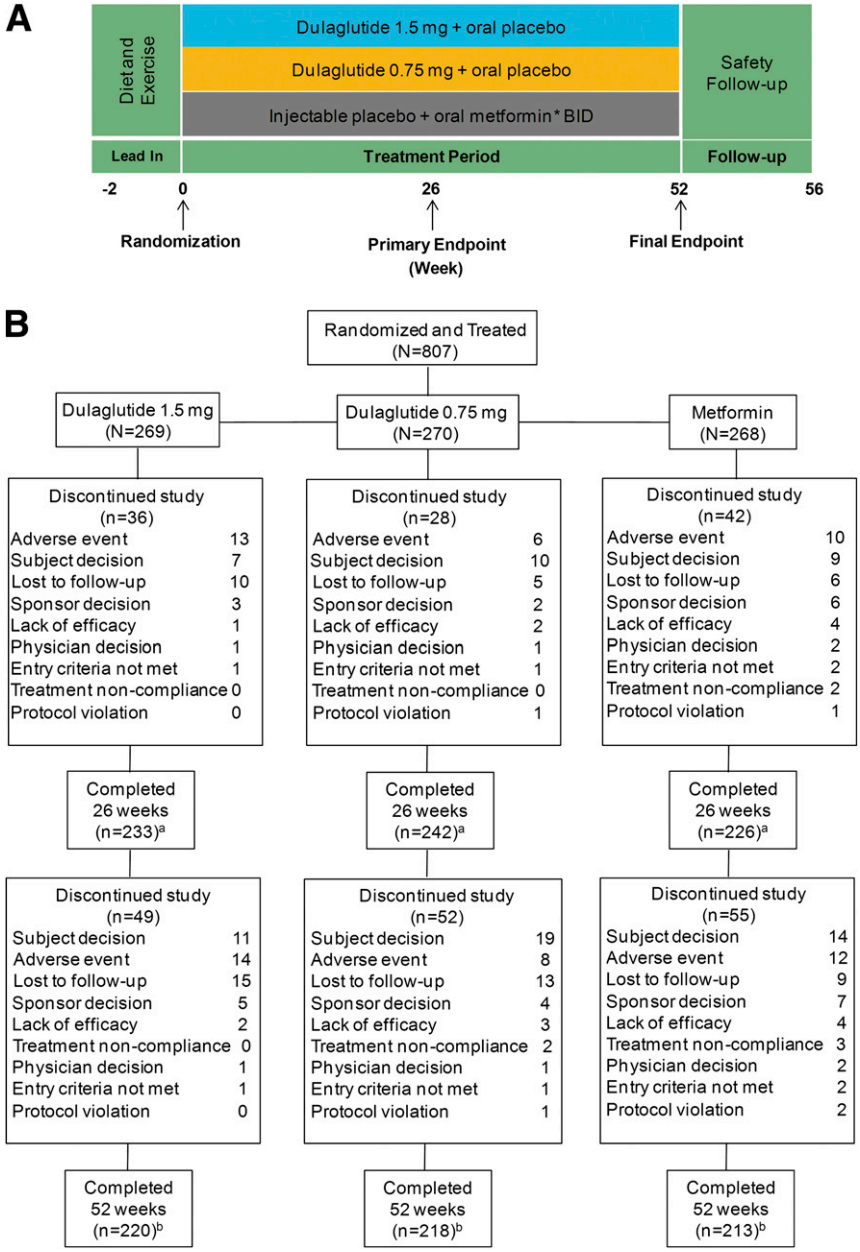

Figure 1—Study design (*A*) and patient disposition (*B*). (*A*) *Patients received 2,000 or 1,500 mg/day according to tolerability. (*B*) Patients discontinued at week 26 are also included as discontinued at week 52. [a]Number of patients rescued at week 26 for severe, persistent hyperglycemia: dulaglutide 1.5 mg, 6 (2.2%); dulaglutide 0.75 mg, 6 (2.2%); and metformin, 7 (2.6%). [b]Number of patients rescued at week 52 for severe, persistent hyperglycemia: dulaglutide 1.5 mg, 12 (4.5%); dulaglutide 0.75 mg, 8 (3.0%); and metformin, 14 (5.2%). BID, twice daily.

hypoglycemia (16). Severe hypoglycemia was any episode requiring the assistance of another person to actively administer therapy.

Statistical Analyses

The study was designed with 90% power to detect noninferiority of dulaglutide 1.5 mg versus metformin on HbA_{1c} change from baseline at the 26-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 corresponds to 251 patients per arm, with an assumed dropout rate of 11%. If noninferiority was met, superiority was assessed using a tree-gatekeeping approach in which the type I error rate across all treatment comparisons for change from baseline in HbA_{1c} at 26 weeks was strongly controlled at 0.025 (one-sided) (17). *P* values were adjusted so that each can be compared with 0.025 to assess significance while accounting for multiplicity adjustments (18). The analyses of efficacy and safety were based on the intent-to-treat population consisting of all randomized patients who received at least one dose of study treatment. For the assessment of efficacy and hypoglycemia, only data obtained prior to rescue medication were used.

The change from baseline in HbA_{1c} and weight at 26 and 52 weeks was analyzed using ANCOVA with factors for treatment, country, and prior diabetes-medication usage (yes/no) with the baseline value as a covariate. The last

observation was carried forward (LOCF) for missing data. A mixed-effects, repeated-measures (MMRM) analysis with additional factors for visit and treatment-by-visit interaction and patient as a random effect was used for assessment of other continuous secondary end points, as well as for sensitivity analyses of HbA_{1c} and weight over time. The percentage of patients achieving HbA_{1c} targets (LOCF) was analyzed 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 (16). The percentage of patients experiencing adverse events was analyzed using a χ^2 test, unless there were not 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 807 randomized patients were treated with at least one dose of study drug and comprised the intent-to-treat population. Demographic and baseline characteristics were similar between treatment arms (Table 1). Approximately 75% of patients were on low-dose OAM monotherapy at screening. Of those patients, ~90% were treated with metformin. Study withdrawal rates were similar between treatment arms at 26 and 52 weeks, with the most frequent reasons being adverse events, subject decision, and lost to follow-up (Fig. 1*B*). At weeks 26 and 52, ~85% of patients in the metformin treatment arm were taking 2,000 mg/day.

Efficacy

At the 26-week primary end point, reductions from baseline in HbA_{1c} were (least squares [LS] mean ± SE): dulaglutide 1.5 mg, −0.78 ± 0.06% (−8.5 ± 0.7 mmol/mol); dulaglutide 0.75 mg, −0.71 ± 0.06% (−7.8 ± 0.7 mmol/mol); and metformin, −0.56 ± 0.06% (−6.1 ± 0.7 mmol/mol) (Fig. 2*A*). Dulaglutide 1.5 mg resulted in a greater HbA_{1c} change compared with metformin (LS mean difference [nominal 95% CI]: −0.22% [−0.36 to −0.08] [−2.4 mmol/mol; −3.93 to −0.87]; adjusted P = 0.002). Dulaglutide 0.75 mg was also associated with a greater HbA_{1c} decrease versus metformin: −0.15% (−1.6 mmol/mol; adjusted P = 0.020). The improvement in HbA_{1c} was observed in patients previously treated with OAM monotherapy (combined treatment group mean ± SD HbA_{1c} reduction −0.50 ± 0.95% [−5.5 ± 10.4 mmol/mol]) and in those treated with diet only (−0.86 ± 0.79% [−9.4 ± 8.6 mmol/mol]). Treatment differences between dulaglutide arms and metformin were consistent within the two subgroups (treatment-by-OAM status interaction P = 0.80) (Supplementary Material). Similarly at 52 weeks, LS mean HbA_{1c} decreased from baseline in all treatment arms (dulaglutide 1.5 mg, −0.70 ± 0.07% [−7.7 ± 0.8 mmol/mol]; dulaglutide 0.75 mg, −0.55 ± 0.07% [−6.0 ± 0.8 mmol/mol]; and metformin, −0.51 ± 0.07% [−5.6 ± 0.8 mmol/mol]). Compared with metformin, the HbA_{1c} reduction was greater with dulaglutide 1.5 mg (adjusted P = 0.02) and similar with dulaglutide 0.75 mg. In MMRM sensitivity analyses at 26 weeks, dulaglutide 1.5 mg was superior to metformin, while dulaglutide 0.75 mg was noninferior;

Table 1—Baseline characteristics and demographics of patients

Variable	Dulaglutide 1.5 mg (n = 269)	Dulaglutide 0.75 mg (n = 270)	Metformin (n = 268)
Sex, *n* (%)			
Men	114 (42)	118 (44)	121 (45)
Women	155 (58)	152 (56)	147 (55)
Age (years)	56 ± 10	56 ± 11	55 ± 10
Race, *n* (%)			
American Indian or Alaskan native	29 (11)	28 (10)	28 (10)
Asian	21 (8)	20 (7)	20 (8)
Black or African American	17 (6)	22 (8)	14 (5)
Multiple	1 (<1)	2 (1)	4 (2)
Native Hawaiian or other Pacific Islander	0 (0)	0 (0)	1 (<1)
White	201 (75)	198 (73)	201 (75)
Ethnicity, *n* (%)			
Hispanic	90 (33)	87 (32)	95 (35)
Non-Hispanic	179 (67)	183 (68)	173 (65)
Weight (kg)	93 ± 19	92 ± 19	92 ± 19
BMI (kg/m^2)	34 ± 6	33 ± 6	33 ± 5
Diabetes duration (years)	3 ± 2	3 ± 2	3 ± 2
HbA_{1c} (%)	7.6 ± 0.9	7.6 ± 0.9	7.6 ± 0.8
HbA_{1c} (mmol/mol)	59.6 ± 10	59.6 ± 10	59.6 ± 9
FSG (mg/dL)	164 ± 50	161 ± 47	161 ± 43
Prestudy treatment (%)[a]			
No OAM	24.9	25.6	24.3
1 OAM	75.1	74.4	75.7
SBP (mm Hg)	130 ± 16	130 ± 16	129 ± 16
DBP (mm Hg)	79 ± 9	80 ± 10	80 ± 10

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

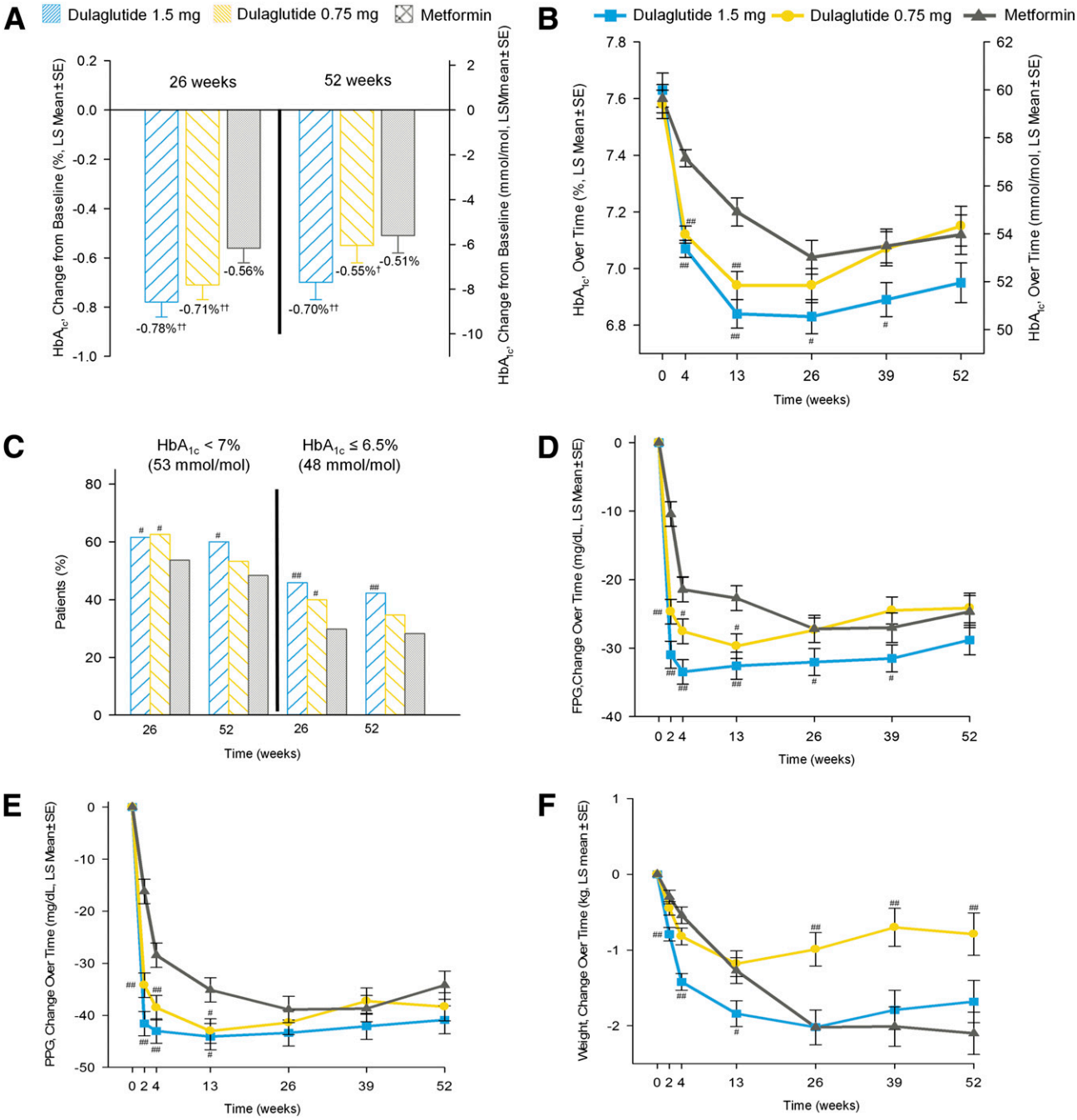

Figure 2—Efficacy measures through the treatment period. *A*: Change in HbA_{1c} from baseline, ANCOVA LOCF. *B*: HbA_{1c} over time, MMRM. *C*: Percentage of patients achieving HbA_{1c} targets at 26 and 52 weeks, logistic regression. *D*: Change from baseline in SMPG fasting plasma glucose (FPG) over time, MMRM. *E*: Change from baseline in SMPG postprandial glucose (PPG; mean of three meals) over time, MMRM. *F*: Weight change from baseline over time, MMRM. †$P < 0.025$, noninferiority vs. metformin; ††$P < 0.025$, superiority vs. metformin; #$P < 0.05$ vs. metformin; ##$P < 0.001$ vs. metformin.

at 52 weeks, both doses were noninferior to metformin (Fig. 2*B*).

More patients reached the HbA_{1c} target of <7.0% (<53 mmol/mol) with both dulaglutide 1.5 mg (62%) and dulaglutide 0.75 mg (63%) compared with metformin (54%) at 26 weeks (P = 0.02, both comparisons) (Fig. 2*C*). At the same time point, more patients also achieved an HbA_{1c} ≤6.5% (≤48 mmol/mol) with dulaglutide 1.5 mg (46%) and dulaglutide 0.75 mg (40%) versus metformin (30%) ($P < 0.001$ and P = 0.011, respectively). The percentage of patients <7.0% (<53 mmol/mol) and ≤6.5% (≤48 mmol/mol) was maintained at 52 weeks with dulaglutide 1.5 mg and continued to be greater than metformin ($P \leq 0.001$, both comparisons). Dulaglutide 0.75 mg and metformin did not differ in the percentages of patients reaching targets at this time point.

The magnitude of decrease in LS mean FSG using central laboratory values in the dulaglutide 1.5 mg, dulaglutide 0.75 mg, and metformin arms was similar at 26

weeks (−29 ± 2, −26 ± 2, and −24 ± 2 mg/dL, respectively). At 52 weeks, changes from baseline in FSG were −28 ± 3, −18 ± 3, and −21 ± 3 mg/dL, respectively; the reduction was greater for dulaglutide 1.5 mg compared with metformin (P = 0.025).

Changes in the eight-point SMPG profiles in the three treatment groups (Supplementary Material) were consistent with changes in HbA_{1c}. Decreases in mean fasting and postprandial glucose were observed over time (Fig. 2*D* and *E*). In all three treatment arms, improvements from baseline were noted in the mean of all preprandial glucose values (LS mean ± SE: −29.9 ± 2.2, −28.6 ± 2.0, and −25.2 ± 2.2 mg/dL with dulaglutide 1.5 mg, dulaglutide 0.75 mg, and metformin, respectively), the mean of all postprandial glucose values (−43.4 ± 2.5, −41.4 ± 2.3, and −38.9 ± 2.5 mg/dL, respectively), and the mean of all glucose excursions (−13.3 ± 1.8, −13.5 ± 1.8, −11.9 ± 1.8 mg/dL, respectively), with no significant difference between dulaglutide and metformin groups at 26 weeks. Similar results were demonstrated at 52 weeks.

Patients in all three treatment arms experienced weight loss over time (Fig. 2*F*). The LS mean change from baseline in body weight at 26 weeks was −2.29 ± 0.24 kg for dulaglutide 1.5 mg, −1.36 ± 0.24 kg for dulaglutide 0.75 mg, and −2.22 ± 0.24 kg for metformin. At 52 weeks, LS mean changes were maintained across treatment groups. Compared with metformin, decrease in body weight was similar with dulaglutide 1.5 mg and smaller with dulaglutide 0.75 mg at 26 (P = 0.003) and 52 weeks (P = 0.001).

At 26 weeks, HOMA2-%B increased in all treatment arms; changes with dulaglutide 1.5 mg and dulaglutide 0.75 mg were greater than with metformin ($P <$ 0.001, both comparisons) (Supplementary Material). HOMA2-%S also increased in the three arms, with greater changes with metformin compared with dulaglutide (dulaglutide 1.5 mg, P = 0.001; and dulaglutide 0.75 mg; P = 0.010). Results were similar for both indices at 52 weeks, with the exception that the difference in HOMA2-%S between dulaglutide 1.5 mg and metformin was no longer significant. At 26 weeks, fasting glucagon decreased with dulaglutide 1.5 mg and dulaglutide 0.75 mg and was unchanged in the metformin group ($P <$ 0.001, both comparisons). At 52 weeks, similar glucagon decreases were observed in the three treatment arms.

Safety

During the entire 52-week treatment period, the incidence of serious adverse events was comparable between treatment arms (Table 2); no deaths occurred during the study. The overall incidence of adverse events was also similar in the three groups (range 63.4–65.6%). The most commonly reported adverse events were nausea (19.7, 11.5, and 16.0% in the dulaglutide 1.5 mg, dulaglutide 0.75 mg, and metformin arms, respectively), diarrhea (11.2, 7.8, and 13.8%), and vomiting (9.7, 7.4, and 4.9%). The majority of these events were mild to moderate in severity and not significantly different between the

Table 2—Safety assessments, change from baseline in vital signs, and treatment-emergent dulaglutide antidrug antibodies

	26 weeks			52 weeks		
Variable	Dulaglutide 1.5 mg (n = 269)	Dulaglutide 0.75 mg (n = 270)	Metformin (n = 268)	Dulaglutide 1.5 mg (n = 269)	Dulaglutide 0.75 mg (n = 270)	Metformin (n = 268)
Death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Serious adverse events[a]	—	—	—	15 (5.6)	20 (7.4)	16 (6.0)
TE adverse events (patients with ≥1 event)	163 (60.6)	150 (55.6)	151 (56.3)	179 (66.5)	177 (65.6)	170 (63.4)
TE adverse events (≥5% patients)						
GI events						
Nausea	51 (19.0)	29 (10.7)	39 (14.6)	53 (19.7)	31 (11.5)	43 (16.0)
Diarrhea	27 (10.0)	14 (5.2)##	37 (13.8)	30 (11.2)	21 (7.8)	37 (13.8)
Vomiting	23 (8.6)	16 (5.9)	11 (4.1)	26 (9.7)	20 (7.4)	13 (4.9)
Decreased appetite	18 (6.7)	11 (4.1)	12 (4.5)	18 (6.7)	12 (4.4)	12 (4.5)
Constipation	17 (6.3)#	9 (3.3)#	2 (0.7)	18 (6.7)#	13 (4.8)#	3 (1.1)
Infections and Infestations						
Nasopharyngitis	10 (3.7)#	7 (2.6)#	21 (7.8)	14 (5.2)#	8 (3.0)#	28 (10.4)
URTI	10 (3.7)	11(4.1)	7 (2.6)	16 (5.9)	15 (5.6)	8 (3.0)
Nervous-system disorders						
Headache	9 (3.3)	14 (5.2)	18 (6.7)	10 (3.7)	14 (5.2)	20 (7.5)
Discontinuation due to an adverse event, n (%)	13 (4.8)	6 (2.2)	10 (3.7)	14 (5.2)	8 (3.0)	12 (4.5)
Vital signs, LS mean ± SE						
SBP (mmHg)	−1.9 ± 0.89	−2.6 ± 0.88	−0.9 ± 0.89	−0.1 ± 0.88	−2.7 ± 0.88	−1.0 ± 0.88
DBP (mmHg)	0.05 ± 0.57	−1.0 ± 0.56	−0.64 ± 0.58	0.3 ± 0.60	−1.4 ± 0.59	−0.4 ± 0.60
Heart rate (bpm)	2.4 ± 0.58	2.1 ± 0.57	1.6 ± 0.58	1.8 ± 0.57	1.6 ± 0.57	1.1 ± 0.57
TE dulaglutide ADA[a], n (%)	—	—	—	6 (2.2)	4 (1.5)	NA

Data are presented as n (%) unless otherwise indicated. ADA, antidrug antibody; DBP, diastolic blood pressure; NA, not applicable; SBP, systolic blood pressure; TE, treatment-emergent; URTI, upper respiratory tract infection. [a]Data were not summarized at 26 weeks. #$P <$ 0.05 vs. metformin. ##$P <$ 0.001 vs. metformin.

groups. At baseline, the mean overall GCSI score was 0.3. At 52 weeks, an increase in the GCSI score (worsening) was observed in all three groups, with LS mean changes from baseline with dulaglutide 1.5 mg of 0.2, dulaglutide 0.75 mg of 0.1, and metformin of 0.2. The rates of discontinuation due to an adverse event were similar across arms (5.2, 3.0, and 4.5% for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and metformin, respectively). Seven patients discontinued the study due to nausea in the dulaglutide 1.5 mg (three patients), dulaglutide 0.75 mg (one patient), and metformin (three patients) arms, the majority before week 26.

Incidence of total hypoglycemia was 12.3% for dulaglutide 1.5 mg, 11.1% for dulaglutide 0.75 mg, and 12.7% for metformin. Rates of total hypoglycemia were 0.89, 0.47, and 0.29 events/patient/year, respectively. No severe hypoglycemic episode occurred.

There were no cases of adjudicated pancreatitis or pancreatic cancer events reported during the study. Increases from baseline in median values of serum lipase, total amylase, and p-amylase that remained within the normal range were observed across both dulaglutide and the metformin arms (Supplementary Material). Compared to metformin, at the end of the entire 52-week treatment period, the incidence of treatment-emergent values above ULN at 52 weeks was higher with dulaglutide 1.5 mg for lipase ($P = 0.001$) and with both dulaglutide 1.5 mg and 0.75 mg for total amylase ($P < 0.05$) (Supplementary Material). There were no changes in the mean calcitonin values throughout the study in any of the treatment arms. No clinically relevant between-treatment differences in other laboratory parameters or electrocardiogram readings were noted.

Changes in systolic and diastolic blood pressure were comparable in the dulaglutide and metformin arms. Increases in heart rate (1–3 bpm) were noted in the three treatment groups with no significant difference between dulaglutide and metformin (Table 2).

In dulaglutide-treatment arms, 2% of patients ($N = 10$) developed treatment-emergent dulaglutide antidrug antibodies (Table 2). Six of them had neutralizing antibodies. The very small number of patients with dulaglutide antidrug antibodies did not support a valid analysis of between-group effects on glycemic control. No patients reported systemic hypersensitivity reactions. Few patients reported injection-site reaction adverse events (dulaglutide 1.5 mg, $n = 10$; dulaglutide 0.75 mg, $n = 6$; and metformin, $n = 4$). In addition, based on a specific Skin Evaluation Checklist (pain, pruritus, and rash at the injection site), <5% of patients reported an event at any given visit in any treatment arm, with no significant between-group differences observed for any item at any visit postbaseline.

CONCLUSIONS

In this double-blind study of 52 weeks' duration, we evaluated the efficacy and safety of monotherapy with once-weekly dulaglutide compared with metformin in patients with early stage type 2 diabetes. Although the between-treatment differences were modest, at the 26-week primary end point of the AWARD-3 trial, dulaglutide was associated with a significantly greater decrease from baseline in HbA_{1c} and a higher percentage of patients reaching clinically relevant HbA_{1c} targets than metformin. Additionally, there was a sustained decrease in body weight in all treatment arms that was similar between dulaglutide 1.5 mg and metformin.

It is noteworthy to observe that in AWARD-3, the magnitude of HbA_{1c} change associated with both dulaglutide and metformin was smaller than generally reported in other monotherapy trials with the same compounds or other compounds of the GLP-1 receptor agonists class (10,19–22). The low mean HbA_{1c} at randomization (7.6% [60 mmol/mol]) in AWARD-3 was a likely contributor to this observation, as it is well established that intervention-induced HbA_{1c} changes are confounded by baseline glycemic status (23,24). In two monotherapy studies of a GLP-1 receptor agonist, the mean baseline HbA_{1c} was 8.3% [67 mmol/mol] in LEAD-3 and 8.5% [69 mmol/mol] in DURATION-4, resulting in HbA_{1c} reductions of −1.14% (−12.5 mmol/mol) for once-daily liraglutide 1.8 mg and −1.53% (−17 mmol/mol) for exenatide once-weekly (25,26). However, the mean end point HbA_{1c} and the percentage of patients achieving HbA_{1c} targets with dulaglutide in AWARD-3 was comparable to that observed in both of these two studies. This is not surprising, since the effect of GLP-1 receptor agonists on the β-cell, the primary glucose-lowering mechanism, is dependent on hyperglycemia levels.

The relatively short washout period may have also contributed to the magnitude of the HbA_{1c} change in our trial, given that 75% of patients were on OAM monotherapy prior to study entry (Supplementary Material). In a previous phase 2 dulaglutide monotherapy trial with a longer washout period (≥8 weeks), the HbA_{1c} change from baseline after 12 weeks of treatment with dulaglutide 1.5 mg was greater despite similar baseline HbA_{1c} to that in AWARD-3 (10). It would be expected that a longer preintervention washout phase enables a more accurate assessment of within-group treatment effect, due to lack of interference of prestudy treatment on baseline HbA_{1c}. The short washout in AWARD-3, however, did not have an impact on the outcome of the prespecified comparisons, as indicated by the differences observed between treatments among the patient subgroups (diet only or OAM monotherapy). This subgroup analysis also indicates that there was no significant impact of the specific prestudy therapy on the results in either dulaglutide or metformin arms, despite the fact that the majority of patients who were on a prior OAM had been receiving biguanides at half-maximal or less dosing before screening.

The near-maximal effect of dulaglutide on plasma glucose was evident at the first follow-up visit, 2 weeks after therapy initiation. This is consistent with the known pharmacokinetic characteristics of dulaglutide, including the peak activity at 12–72 h after dose administration with steady state reached after 2 to 3 weeks (9). Dulaglutide decreased both fasting and postprandial glucose; the concurrent reduction in postprandial glucose excursions by ~40% indicates that dulaglutide improves glucose control after meals, at least in part, independently of its effect on preprandial glycemia.

Both treatments were associated with increases in HOMA2-%B and HOMA2-%S indices and decreases in glucagon concentrations, but patterns

were different. While interpretation of HOMA indexes requires caution, significantly greater improvements in HOMA2-%B and significantly smaller effects on HOMA2-%S with dulaglutide seem to confirm that the predominant glucose-lowering mechanism of dulaglutide relates to enhancement of pancreatic β-cell function; since this effect is glucose dependent, the frequency of hypoglycemia in AWARD-3 was very low. Decrease in glucagon concentrations and improvement in insulin sensitivity may be additional contributors to glycemic control in these patients, consistent with similar effects described with other agents from the class (26). Inversely, metformin's effect appears to be mainly explained by an improvement in peripheral insulin sensitivity and, to a lesser extent, in insulin secretion and decreased glucagon levels. It is of potential clinical relevance that the glucagon-lowering effect of dulaglutide was observed much earlier than with metformin.

Dulaglutide 1.5 mg and metformin were both associated with a similar weight loss of ~2 kg. These results are in line with those reported in another monotherapy study with dulaglutide, as well as with other GLP-1 receptor agonists and metformin (10,25,26). The effect of dulaglutide on body weight in AWARD-3 was clearly dose dependent and explains the greater weight loss with metformin than with dulaglutide 0.75 mg. Weight changes were maintained through the full 52-week duration of the study.

Nausea, vomiting, and diarrhea are known side effects of metformin and the GLP-1 receptor agonist class (26–28). In this study, GI symptoms associated with dulaglutide were of similar frequency to metformin, and most of the cases were mild to moderate in severity, rarely resulting in study discontinuation. Very small changes in GCSI scores confirmed that the severity of GI symptoms was acceptable for both dulaglutide and metformin. A GI tolerability profile, which is similar to that of a widely used medication like metformin, is important information to be considered by patients and physicians when making a therapeutic decision.

Small elevations in pancreatic enzymes (lipase, total amylase, and p-amylase) were observed over time, regardless of whether the patient was treated with dulaglutide or metformin, but were greater in association with dulaglutide. This finding is consistent with elevations observed with other GLP-1 receptor agonists (29–31). While the specific cause of this effect on pancreatic enzymes is not well understood, it has been proposed that GLP-1 receptor agonists may directly interact with the exocrine pancreas, leading to enzyme elevations (32). Regarding metformin, to our knowledge, there are no previously reported data based on measurement of serial pancreatic enzymes in metformin-treated patients. Increases in these laboratory analytes in the absence of other symptoms (i.e., abdominal pain, severe nausea, and/or vomiting) are not predictive of acute pancreatitis. This is supported by the absence of adjudicated events of acute pancreatitis, including in patients with the greatest observed changes (≥3 times ULN) (Supplementary Material).

The immunogenicity of dulaglutide was low, with very few patients developing treatment-emergent dulaglutide antidrug antibody titers, and these were not associated with relevant hypersensitivity events; no difference in incidences of local or systemic hypersensitivity adverse events between treatment groups was observed. Not unexpectedly, dulaglutide induced a small increase in heart rate (1–3 bpm). This effect is common among the GLP-1 receptor agonist class (33). The clinical relevance of this increase in heart rate is unknown.

In conclusion, in this 52-week double-blind study in patients with early stage type 2 diabetes, monotherapy with once-weekly dulaglutide resulted in early reductions from baseline in HbA_{1c} and a higher percentage of patients reaching clinically relevant HbA_{1c} targets compared with metformin. The tolerability profile for dulaglutide was similar to metformin, and safety was comparable to the GLP-1 receptor agonist class. Use of once-weekly dulaglutide is a clinically appropriate monotherapy option for some patients with type 2 diabetes who are not considered optimal candidates for metformin therapy.

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Author Contributions. G.U., S.T.P., and F.P.M. researched data, contributed to the discussion, and reviewed and edited the manuscript. L.S. and V.P. researched data and wrote the manuscript. V.P. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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SUPPLEMENTARY DATA

Supplementary Table 1. Other endpoints of interest, change from baseline at 26 and 52 weeks.

	26 weeks		52 weeks			
Metabolic Parameters	Dulaglutide 1.5 mg (n=269)	Dulaglutide 0.75 mg (n=270)	Metformin (n=268)	Dulaglutide 1.5 mg (n=269)	Dulaglutide 0.75 mg (n=270)	Metformin (n=268)
Fasting insulin (pmol/L)	17.5 ± 9.7[#]	35.4 ± 9.6[#]	-20.5 ± 9.5	6.1 ± 9.5[#]	31.5 ± 9.4[##]	-23.0 ± 9.6
Fasting C-peptide (nmol/L)	0.07 ± 0.04[##]	0.09 ± 0.03[##]	-0.11± 0.03	0.06 ± 0.04[##]	0.14 ± 0.04[##]	-0.11± 0.04
Fasting proinsulin	-9.0 ± 2.1	-3.0 ± 2.1[##]	-12.0 ± 2.1	-7.3 ± 2.0[#]	-5.3 ± 2.0[#]	-12.6 ± 2.0
HOMA2-%B	36.6 ± 3.4[##]	29.0 ± 3.4[##]	14.1 ± 3.4	30.0 ± 3.5[##]	22.6 ± 3.5[#]	9.8 ± 3.5
HOMA2-%S	0.12 ± 2.4[##]	1.5 ± 2.4[#]	9.1 ± 2.3	5.2 ± 2.4	2.7 ± 2.4[#]	10.8 ± 2.4
Fasting proinsulin/insulin	-0.11± 0.03	-0.12 ± 0.03	-0.08 ± 0.03	-0.08 ± 0.02	-0.11 ± 0.02	-0.11 ± 0.02
Fasting proinsulin/C-peptide	-8.3 ± 1.2	-5.6 ± 1.2[#]	-9.4 ± 1.2	-7.7 ± 1.0[#]	-7.5 ± 1.0[#]	-10.0 ± 1.0
Fasting glucagon (pmol/L)	-2.1 ± 0.44[##]	-1.7 ± 0.44[##]	0.2 ± 0.44	-2.1 ± 0.46	-2.2 ± 0.46	-1.4 ± 0.47
Lipids Parameters, median % change from baseline [Q1,Q3]						
Total cholesterol	-4 [-11, 5]	-2 [-10, 8]	-4 [-12, 5]	-2 [-11, 7]	-1 [-10, 8][#]	-4 [-12, 6]
LDL cholesterol	-7 [-18, 8]	-3 [-15, 9][#]	-9 [-20, 5]	-2 [-16, 9][#]	-2 [-15, 11][#]	-7 [-19, 4]
HDL cholesterol	2 [-4, 14]	4 [-6, 15]	6 [-3, 14]	5 [-5, 13]	2 [-5, 13]	4 [-7, 14]
Triglycerides	-2 [-22, 14][#]	-2 [-22, 23]	3 [-16, 24]	-4 [-23, 19]	-1 [-22, 25]	2 [-22, 24]
Pancreatic Enzymes, median [Q1,Q3] (U/L)						
Lipase	7 [1,16][##]	5 [0,13][##]	1 [-4,8]	5 [-1,13][##]	5 [0,12][##]	1 [-4,6]
Total amylase	7 [2,13][##]	6 [0,13][#]	4 [-2,10]	6 [-1,13]	5 [-1,13]	4 [-2,9]
p-Amylase	5 [2,9][##]	4 [1,7][##]	1 [-1,5]	4 [1,7][##]	3 [0,8][##]	2 [-1,5]
Patients with at least 1 TE abnormality (n, %)[a]						
Lipase	91 (37.6)[#]	76 (30.5)	61 (25.7)	109 (50.0)[##]	91 (41.7)	74 (34.7)
Total Amylase	28 (11.6)	24 (9.6)	14 (5.9)	34 (15.6)[#]	35 (16.1)[#]	16 (7.5)
p-Amylase	33 (13.7)	37 (14.9)	22 (9.3)	42 (19.3)	44 (20.3)	26 (12.2)
Pancreatic Enzymes, n (%) of patients with >3x ULN [b]						
Lipase	2 (0.9)	1 (0.4)	1 (0.5)	1 (0.5)	3 (1.5)	0 (0.0)
p-Amylase	2 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)

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

All data are LS mean ± SE unless otherwise noted. [#]$P < 0.05$ vs metformin; [##]$P \leq 0.001$ vs metformin. Abbreviations: bpm = beats per minute; HOMA2-%B = updated homeostasis model beta cell function; HOMA2-%S = updated homeostasis model insulin sensitivity; p-amylase = pancreas-derived amylase; TE = treatment emergent; $Q_{x=}$ quartile number.

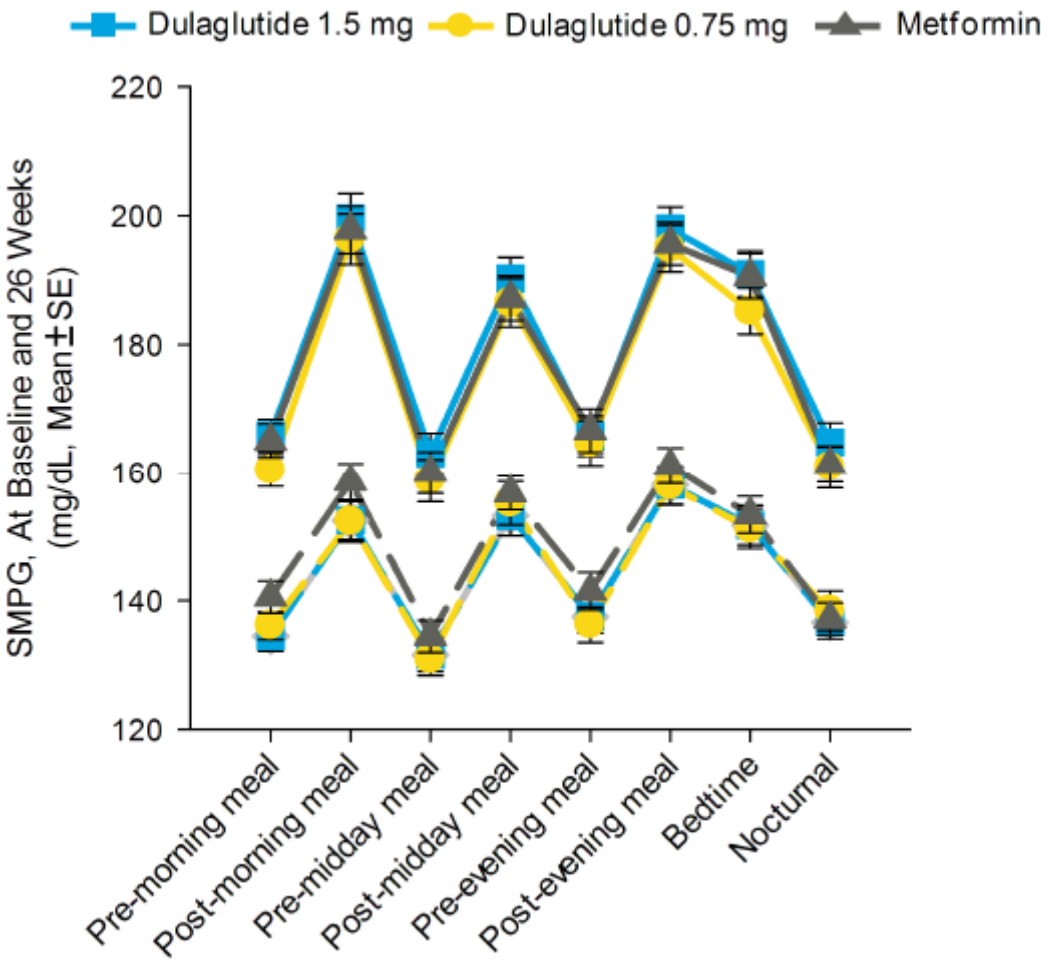
SUPPLEMENTARY DATA

Supplementary Table 2. Baseline HbA_{1c} (%) and change from baseline in HbA_{1c} (%) at 26 weeks in OAM-naïve patients and patients previously treated with one OAM.

	HbA_{1c} (%)	Dulaglutide 1.5 mg	Dulaglutide 0.75 mg	Metformin	Total
No OAM	n	67	69	65	201
	Baseline	7.55 ± 0.95	7.46 ± 0.98	7.36 ± 0.71	7.46 ± 0.89
	Change from baseline	-1.05 ± 0.77	-0.86 ± 0.78	-0.67 ± 0.80	-0.86 ± 0.79[#]
OAM	n	202	201	203	606
	Baseline	7.65 ± 0.90	7.62 ± 0.83	7.68 ±0.84	7.65 ± 0.86
	Change from baseline	-0.58 ± 0.93	-0.50 ± 0.95	-0.40 ± 0.97	-0.50 ± 0.95

SUPPLEMENTARY DATA

Supplementary Figure 1. Baseline and 26 week eight-point SMPG profiles. Solid lines are baseline and dashed lines are 26 Week. ANCOVA using LOCF.



SUPPLEMENTARY DATA

Supplementary Table 1. Other endpoints of interest, change from baseline at 26 and 52 weeks.

	26 weeks		52 weeks			
Metabolic Parameters	Dulaglutide 1.5 mg (n=269)	Dulaglutide 0.75 mg (n=270)	Metformin (n=268)	Dulaglutide 1.5 mg (n=269)	Dulaglutide 0.75 mg (n=270)	Metformin (n=268)
Fasting insulin (pmol/L)	17.5 ± 9.7[#]	35.4 ± 9.6[#]	-20.5 ± 9.5	6.1 ± 9.5[#]	31.5 ± 9.4[##]	-23.0 ± 9.6
Fasting C-peptide (nmol/L)	0.07 ± 0.04[##]	0.09 ± 0.03[##]	-0.11± 0.03	0.06 ± 0.04[##]	0.14 ± 0.04[##]	-0.11± 0.04
Fasting proinsulin	-9.0 ± 2.1	-3.0 ± 2.1[##]	-12.0 ± 2.1	-7.3 ± 2.0[#]	-5.3 ± 2.0[#]	-12.6 ± 2.0
HOMA2-%B	36.6 ± 3.4[##]	29.0 ± 3.4[##]	14.1 ± 3.4	30.0 ± 3.5[##]	22.6 ± 3.5[#]	9.8 ± 3.5
HOMA2-%S	0.12 ± 2.4[##]	1.5 ± 2.4[#]	9.1 ± 2.3	5.2 ± 2.4	2.7 ± 2.4[#]	10.8 ± 2.4
Fasting proinsulin/insulin	-0.11± 0.03	-0.12 ± 0.03	-0.08 ± 0.03	-0.08 ± 0.02	-0.11 ± 0.02	-0.11 ± 0.02
Fasting proinsulin/C-peptide	-8.3 ± 1.2	-5.6 ± 1.2[#]	-9.4 ± 1.2	-7.7 ± 1.0[#]	-7.5 ± 1.0[#]	-10.0 ± 1.0
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Lipids Parameters, median % change from baseline [Q1,Q3]						
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HDL cholesterol	2 [-4, 14]	4 [-6, 15]	6 [-3, 14]	5 [-5, 13]	2 [-5, 13]	4 [-7, 14]
Triglycerides	-2 [-22, 14][#]	-2 [-22, 23]	3 [-16, 24]	-4 [-23, 19]	-1 [-22, 25]	2 [-22, 24]
Pancreatic Enzymes, median [Q1,Q3] (U/L)						
Lipase	7 [1,16][##]	5 [0,13][##]	1 [-4,8]	5 [-1,13][##]	5 [0,12][##]	1 [-4,6]
Total amylase	7 [2,13][##]	6 [0,13][#]	4 [-2,10]	6 [-1,13]	5 [-1,13]	4 [-2,9]
p-Amylase	5 [2,9][##]	4 [1,7][##]	1 [-1,5]	4 [1,7][##]	3 [0,8][##]	2 [-1,5]
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Lipase	2 (0.9)	1 (0.4)	1 (0.5)	1 (0.5)	3 (1.5)	0 (0.0)
p-Amylase	2 (0.8)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)

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

All data are LS mean ± SE unless otherwise noted. [#]$P < 0.05$ vs metformin; [##]$P \leq 0.001$ vs metformin. Abbreviations: bpm = beats per minute; HOMA2-%B = updated homeostasis model beta cell function; HOMA2-%S = updated homeostasis model insulin sensitivity; p-amylase = pancreas-derived amylase; TE = treatment emergent; $Q_{x=}$ quartile number.

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	Baseline	7.65 ± 0.90	7.62 ± 0.83	7.68 ±0.84	7.65 ± 0.86
	Change from baseline	-0.58 ± 0.93	-0.50 ± 0.95	-0.40 ± 0.97	-0.50 ± 0.95

SUPPLEMENTARY DATA

Supplementary Figure 1. Baseline and 26 week eight-point SMPG profiles. Solid lines are baseline and dashed lines are 26 Week. ANCOVA using LOCF.