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

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ABSTRACT

Objective: To compare efficacy and safety of dulaglutide, a once weekly glucagon-like peptide1 receptor agonist, to placebo and exenatide in type 2 diabetes patients. Primary objective was superiority of dulaglutide 1.5 mg versus placebo in HbA\textsubscript{1c} change at 26 weeks.

Research Design and Methods: This 52-week, multicenter, parallel-arm study (primary endpoint: 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 (1500-3000 mg) and pioglitazone (30-45 mg); mean baseline HbA\textsubscript{1c} was 8.1% (65 mmol/mol).

Results: LS mean (± SE) HbA\textsubscript{1c} change from baseline to primary endpoint 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, -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-values < 0.001), and exenatide at 26 and 52 weeks (both adjusted one-sided P-values <0.001). Greater percentages reached HbA\textsubscript{1c} targets with dulaglutide 1.5 mg and 0.75 mg compared to placebo and exenatide (P < 0.001, all). At 26 and at 52 weeks, total hypoglycemia incidence was lower in the dulaglutide 1.5 mg compared to exenatide; no dulaglutide-treated patients reported severe hypoglycemia. 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.

Key words: HbA$_{1c}$, dulaglutide, GLP-1, GLP-1 receptor agonist, exenatide, type 2 diabetes, AWARD-1

Abbreviations

HbA$_{1c}$: glycosylated hemoglobin A$_{1c}$; ADA: anti-drug antibody; bpm: beats per minute; DBP: diastolic blood pressure; DPP-4: dipeptidyl peptidase-4; DU: dulaglutide; EX: exenatide; FSG: fasting serum glucose; GI: gastrointestinal; GLP-1: glucagon-like peptide 1; HOMA2: updated homeostasis model assessment; HOMA2-%B: homeostasis model assessment of β-cell function; HOMA2-%S: homeostasis model assessment of insulin sensitivity; IDF: International Diabetes Federation; ITT: intent-to-treat; LS: least squares; LOCF: last observation carried forward; MMRM: mixed-model repeated measures; OAM: oral antihyperglycemic medication; p-amylase: pancreatic amylase; PG: plasma glucose; PL: placebo; SBP: systolic blood pressure; SE: standard error; SMPG: self-monitored plasma glucose; TE: treatment emergent; URI: upper respiratory infection; UTI: urinary tract infection.
INTRODUCTION

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, dipeptidyl peptidase-4 (DPP-4) inhibitor may be used (1). While 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 consists of two identical, disulfide-linked chains, each containing an N-terminal GLP-1 analog sequence covalently linked to a modified human immunoglobulin G4 (IgG4) Fc fragment by a small peptide linker (6). In contrast to native GLP-1, dulaglutide is resistant to degradation by DPP-4 and has a large size that slows absorption and reduces renal clearance. The molecular features result in a soluble formulation and a prolonged half-life of approximately 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 Assessment-1) was to compare once weekly dulaglutide to placebo and to exenatide twice daily (exenatide BID [referred to hereafter as exenatide]) in patients with type 2 diabetes treated with maximally tolerated doses of metformin and pioglitazone. This study comparing a short acting GLP-1 receptor agonist and a long acting one, with sustained GLP-1 activation, allows a direct comparison of efficacy and safety profiles. 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, with a BMI ≥23 and ≤45 kg/m², and glycosylated hemoglobin A₁c (HbA₁c) ≥7.0% (53 mmol/mol) and ≤11.0% (97 mmol/mol) on oral antihyperglycemic medication (OAM) monotherapy, or ≥7.0% (53 mmol/mol) and ≤10.0% (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 prior to screening or were on chronic 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 guideline on good clinical practices (8).

Eligible patients entered a lead-in period that lasted up to 12 weeks (Fig. 1A). During this period, previous OAMs other than metformin and pioglitazone were
discontinued, and patients were up-titrated on a dual-OAM regimen of maximally tolerated metformin (≥1500 to ≤3000 mg/day; >2550 mg/day allowed only in certain countries outside of the United States per country label) and pioglitazone (≥30 to ≤45 mg/day). Patients were then stabilized for approximately 8 weeks prior to randomization, at which time a qualifying HbA\textsubscript{1c} >6.5% was required for ongoing eligibility.

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

The primary outcome measure was change in HbA\textsubscript{1c} from baseline to 26 weeks. Secondary efficacy measures included change in HbA\textsubscript{1c} from baseline to 52 weeks, percentage of patients with HbA\textsubscript{1c} <7.0% (53 mmol/mol) or ≤6.5% (48 mmol/mol), changes in central lab fasting serum glucose (FSG), eight-point self-monitored plasma
glucose (SMPG) profiles, change in body weight, and β-cell function and insulin sensitivity indices (updated Homeostasis Model Assessment [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 anti-drug antibodies (ADA). 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 cases of asymptomatic confirmed elevations (≥3x upper limit of normal) in pancreatic enzymes. Laboratory analyses were performed at a central laboratory (Quintiles Laboratories). Immunogenicity testing was performed by BioAgilytix (St. Louis, MO, USA) and Millipore (Durham, NC, USA).

Hypoglycemia was defined as plasma glucose (PG) ≤70 mg/dL (≤3.9 mmol/L) and/or symptoms and/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$_1$c at the 26-week primary endpoint with a standard deviation of 1.3%, a 1-sided alpha of 0.025, and a noninferiority margin of 0.40%. This corresponds to 280 patients per active treatment arm and 140 for placebo, with an assumed drop-out 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 (1-sided) by tree-gatekeeping (10). P-values were adjusted so that each could be compared to 0.025 to assess significance while accounting for multiplicity adjustments (11).

The analyses of efficacy and safety 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 and hypoglycemia events, only data obtained prior to the initiation of 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 the baseline value as a covariate. The last observation was carried forward (LOCF) in the case of missing data. Secondary analysis methods for HbA$_1c$ and weight, and methods for other continuous secondary endpoints 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 standard errors (SE) are reported. 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 (9). The percentage of patients experiencing adverse events was analyzed using a chi-squared test, unless there were not sufficient data to meet the assumptions of the analysis, in which case a Fisher’s exact test was conducted. The 2-sided significance level was 0.05 for secondary endpoints 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 administer drug, thus the ITT population comprised 976 patients. Demographic and baseline characteristics were balanced across all arms (Table 1). At randomization, 86% of patients were receiving ≥2500 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%); placebo, 17 (12.1%). The most common reasons for study discontinuation at 26 weeks were adverse events and subject decision (Fig. 1B). Disposition, including patients receiving rescue therapy, through the overall 52 week study period is presented in Figure 1B.

Efficacy

The LS mean ± SE HbA1c change from baseline to 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. 2A). Dulaglutide 1.5 mg and 0.75 mg doses 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) and -0.84% (-9.2 mmol/mol); -1.01 to -0.67% (-11.0 to -7.3 mmol/mol), respectively. Compared to 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 also 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\textsubscript{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. 2A).
Compared to 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). Fig. 2B shows HbA\textsubscript{1c} values at
baseline and over time up to 52 weeks.

At 26 weeks, the percentage of patients attaining the HbA\textsubscript{1c} goal of <7.0% (53
mmol/mol) was significantly higher in the dulaglutide 1.5 mg and 0.75 mg arms (78% and
66%, respectively) compared to exenatide (52%) (\( P < 0.001 \), both comparisons) and
placebo (43%) (\( P < 0.001 \), both comparisons) (Fig. 2C). At the same time point,
63% and 53% of dulaglutide 1.5 mg and dulaglutide 0.75 mg patients, respectively,
achieved an HbA\textsubscript{1c} target of ≤6.5% (48 mmol/mol), compared to 38% in the exenatide
arm and 24% in the placebo arm (\( P < 0.001 \), all comparisons). At 52 weeks, similar and
consistent effects across and between treatment arms were observed (Fig. 2C).

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

Fig. 2E shows the mean of each PG value from the eight-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 to placebo and exenatide ($P < 0.001$, both comparisons). All active treatment arms had significantly greater LS mean reductions in postprandial PG compared to placebo ($P < 0.001$, all comparisons). Patients on dulaglutide 1.5 mg had a significantly greater reduction in the mean of all postprandial PG values compared to exenatide ($P = 0.047$). Patients on dulaglutide 1.5 mg and exenatide demonstrated greater reductions in the mean of all 2-hour postprandial PG excursions compared to placebo ($P = 0.003$, dulaglutide 1.5 mg; $P < 0.001$, exenatide), with changes in the exenatide group significantly greater compared to the dulaglutide doses ($P < 0.001$, both comparisons). All three active treatment arms exhibited similar reductions in the morning meal postprandial PG. Compared to exenatide at the midday meal, LS mean reductions in postprandial PG were significantly greater for dulaglutide 1.5 mg and 0.75 mg ($P < 0.001$, $P = 0.049$, respectively). At the evening meal, LS mean reduction in postprandial PG was significantly greater for dulaglutide 1.5 mg compared to 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. 2F). Compared to placebo, change in weight with dulaglutide 1.5 mg, dulaglutide 0.75 mg and exenatide was significantly different ($P < 0.001$, $P = 0.010$, and $P < 0.001$, respectively). Compared to 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, $P = 0.474$, dulaglutide 1.5 mg; 1.27 kg, $P < 0.001$, dulaglutide 0.75 mg). The observed differences in weight between the dulaglutide groups and exenatide group were maintained at 52 weeks (Fig 2F).

Pancreatic β-cell function, as measured by HOMA2-%B at 26 weeks, increased with all active treatment arms compared to placebo, and increased more with dulaglutide 1.5 mg compared to 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 (Supplemental Material). Dulaglutide 1.5 mg-treated patients demonstrated a significant mean reduction from baseline in total and LDL cholesterol levels compared to placebo at 26 weeks (Supplemental Material). These patients also demonstrated a significant reduction in mean triglyceride levels as compared to 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 values.

Safety
The incidence of serious adverse events was similar across treatment arms (Table 2). There were two deaths during the study (dulaglutide 1.5 mg: 1 [myocardial infarction]; dulaglutide 0.75 mg: 1 [natural causes; patient had a history of cardiovascular risk factors]); 90 and 102 days, respectively, postrandomization. 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 events in dulaglutide and exenatide-treated patients; nausea and vomiting events were significantly ($P < 0.05$, all comparisons) higher in dulaglutide- and exenatide-treated patients compared to placebo-treated patients at 26 weeks. The incidence of these events was similar among dulaglutide 1.5 mg- and exenatide-treated patients, and significantly ($P < 0.05$, all comparisons) lower with dulaglutide 0.75 mg-treated patients 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 two weeks of treatment with both doses of dulaglutide (Fig. 2G).

Discontinuations due to adverse events were similar across treatment arms at 26 and 52 weeks (Fig. 1B). The most common adverse event leading to discontinuation was nausea (dulaglutide 1.5 mg: 3; dulaglutide 0.75 mg: 1; exenatide: 4). One patient from the dulaglutide 1.5 mg arm was diagnosed with chronic pancreatitis approximately 7 months after study drug initiation. This patient had no signs or symptoms of pancreatitis prior to 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 study off of study drug.

A total of 108 patients (dulaglutide 1.5 mg: 10.4%; dulaglutide 0.75 mg: 10.7%; exenatide: 15.9%; and placebo: 3.5%) experienced hypoglycemia during the first 26 weeks, with significantly fewer patients in the dulaglutide 1.5 mg arm compared to the exenatide arm ($P = 0.007$, at 26 weeks). 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 the dulaglutide 1.5 mg compared to exenatide at 52 weeks. There were no events of severe hypoglycemia among dulaglutide-treated patients, and 2 events were reported for exenatide-treated patients.

Small median increases in serum lipase, total amylase, and pancreatic amylase (p-amylase) that remained within the normal range were observed for dulaglutide and exenatide; these changes were significant ($P < 0.05$, all comparisons) compared to placebo (Supplemental Material). Increases in pancreatic enzymes were greater for dulaglutide 1.5 mg compared to exenatide at 26 weeks, and were also 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 active treatments compared to placebo at 26 weeks, and between active treatments at 52 weeks (Supplemental Material). 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 weeks 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 weeks or 52 weeks (Table 2). Dulaglutide 1.5 mg and dulaglutide 0.75 mg doses were associated with significantly ($P < 0.05$, all comparisons) greater LS mean increases in heart rate at 26 weeks compared to exenatide and placebo; no differences between dulaglutide and exenatide were noted at 52 weeks (Table 2).

A total of 10 patients (1.8%) randomized to dulaglutide developed treatment emergent (TE) dulaglutide ADA at least once postbaseline during the 52-week study (Table 2). Another three patients who were randomized to placebo developed treatment emergent dulaglutide ADA after switching to dulaglutide at 26 weeks. One dulaglutide 1.5 mg-treated patient with treatment emergent dulaglutide ADA experienced local injection site erythema and swelling of 1-day duration. In exenatide-treated patients at 26 weeks, 48% were noted to have treatment emergent exenatide ADA (Table 2). One exenatide-treated patient with treatment emergent exenatide ADA experienced an injection site reaction. No patients reported systemic hypersensitivity reactions.

**Conclusions**

The results of the AWARD-1 study demonstrated that once weekly dulaglutide in combination with maximally tolerated doses of metformin and pioglitazone resulted in significantly larger improvements in HbA$_{1c}$, and percentage of patients achieving target HbA$_{1c}$ goals compared to placebo and active comparator exenatide BID at 26 weeks.
Additionally, dulaglutide 1.5 mg was associated with significant weight reduction compared to placebo. Importantly, the clinically relevant mean difference in HbA$_1c$ change from baseline between dulaglutide and exenatide arms of approximately 0.3-0.5% was achieved with similar or lower risk of hypoglycemia, indicating an acceptable benefit and hypoglycemia risk profile for this new, once weekly GLP-1 receptor agonist.

At randomization, the majority (86%) of patients had tolerated the up-titration 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 addition of a third antihyperglycemic agent. In this population, patients on 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% of patients achieving the goal of $<7.0\%$ (53 mmol/mol); both results superior to exenatide. The previously reported similar glycemic effect of dulaglutide (12) and exenatide (13; 14) compared to placebo provides additional support for the results described here.

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 as compared to exenatide. While both GLP-1 receptor agonists improved preprandial and postprandial blood glucose control as measured on eight-point SMPG profiles, there were some notable differences. Changes from baseline in the mean of all preprandial and the mean of all postprandial PG values were greater with dulaglutide relative to exenatide. Exenatide was associated with a smaller mean postprandial
excursion compared to dulaglutide, likely related to the higher absolute premeal glycemic level with exenatide. Glycemia is the main factor influencing insulin secretion rates in \( \beta \)-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 within the physiologic range, which is believed to result in the observed difference in glucose excursions in this 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. Dulaglutide 1.5 mg- and exenatide-treated patients reported similar incidences of gastrointestinal adverse events, with less frequent reporting in dulaglutide 0.75 mg-treated patients. The incidence of nausea and vomiting also appeared to be similar to the incidence observed with liraglutide when used with similar background therapy (18); nausea was reported by 29% and 40% of patients with liraglutide 1.2 mg and 1.8 mg doses, and vomiting by 7% and 17%, respectively. Overall, fewer dulaglutide-treated patients experienced hypoglycemia compared to exenatide-treated patients. Cardiovascular assessments showed an
increase in systolic blood pressure with placebo compared to dulaglutide and exenatide arms, which may be in part due to 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 upon serial evaluations of thyroid and pancreatic laboratory parameters. The immunogenicity of dulaglutide appeared to be low, with less than 2% of dulaglutide patients developing treatment-emergent anti-drug antibodies, in contrast to 48% incidence in patients exposed to 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 United States in a population that was primarily white and Hispanic.

Overall, it has been shown that once weekly dulaglutide therapy is efficacious and safe in combination with metformin and pioglitazone. Dulaglutide was shown to be superior to placebo and exenatide with respect to HbA1c change from baseline and percentage of patients achieving glycemic targets. Additionally, the observed rapid improvement in fasting glucose and self-monitored glucose values, with an attendant low risk of hypoglycemia, represent an important treatment profile in the management of patients with type 2 diabetes.
**Funding:** This work is sponsored by Eli Lilly and Company. Additional details of this study, entitled “A Study in Patients with Type 2 Diabetes Mellitus (AWARD-1),” can be found at http://clinicaltrials.gov as NCT01064687.

**Author Contributions:** CW researched data, contributed to the discussion, and reviewed/edited the manuscript. TB researched data, contributed to the discussion, and reviewed/edited the manuscript. RA researched data, contributed to the discussion, and reviewed/edited the manuscript. GC researched data, contributed to the discussion, and reviewed/edited the manuscript. PG researched data, contributed to the discussion, and reviewed/edited the manuscript. CA researched data and wrote the manuscript. DK researched data and wrote the manuscript. ML researched data and wrote the manuscript. ML takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

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Ingelheim, Eli Lilly and Company, Janssen, Novo Nordisk, and Sanofi US. TB has received research grants from Amylin Pharmaceuticals, Inc., and served as an advisor and speaker's bureau member for Amylin Pharmaceuticals, Inc. and Eli Lilly and Company. RA has received institutional grants for research from Glaxo Smith Kline, Novartis Pharmaceuticals, Eli Lilly and Company, Reata Pharmaceuticals, and Sanofi-Aventis. RA has received consulting fees from Novo Nordisk Inc. RA has received speaker's fees from Amylin Pharmaceuticals, AstraZeneca, and Bristol Myers Squibb. GC has received consulting fees from Eli Lilly and Company, Sanofi, Quintiles, ad ICON. PG has served as a board member for Novo Nordisk, MSD, and Eli Lilly and Company. GC has received speaker's fees from Bristol Myers Squibb, Eli Lilly and Company, Novo Nordisk Inc., Amgen Inc., and Glaxo Smith Kline. CA, DK, and ML are employees of Eli Lilly and Company. No other conflicts of interest were reported.
Figure Legends

Figure 1. Study Design and Patient Disposition

Study design (A) and patient disposition (B). All patients underwent a metformin (≥1500 to ≤3000 mg/day) and pioglitazone (≥30 to ≤45 mg/day) lead-in period that lasted up to 12 weeks, to be 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 switched 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%).

Figure 2. Efficacy and Safety Measures through the Treatment Period

Change in HbA$_{1c}$ from baseline at 26 and 52 weeks, ANCOVA LOCF (A). HbA$_{1c}$ over time, MMRM (B). Percentage of patients achieving HbA$_{1c}$ targets, logistic regression (C)

Change in FSG over time, MMRM (D) Baseline and 26-week 8-Point SMPG profiles, MMRM; solid lines are baseline and dashed lines are at 26 weeks (E) Change in weight over time, MMRM (F) Incidence of onset of nausea up to 26 weeks (G). Data presented are LS means ± SE. †† $P < 0.001$, superiority vs. exenatide; ‡‡ $P < 0.001$, superiority vs. placebo; #, * $P < 0.05$ vs. exenatide and placebo, respectively; ##, ** $P < 0.001$ vs. exenatide and placebo, respectively. Abbreviations: HbA$_{1c}$ = glycosylated hemoglobin
$\text{A}_{1c}$; FSG = fasting serum glucose; LOCF = last observation carried forward; MMRM:
mixed-model repeated measures SMPG = self-monitored plasma glucose.
References

2. Fineman MS, Bicsak TA, Shen LZ, Taylor K, Gaines E, Varns A, Kim D, Baron AD: Effect on glycemic control of exenatide (synthetic exendin-4) additive to existing metformin and/or sulfonylurea treatment in patients with type 2 diabetes. Diabetes care 2003;26:2370-2377
Table 1. Baseline characteristics and demographics of patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>DU 1.5 mg (N=279)</th>
<th>DU 0.75 mg (N=280)</th>
<th>EX (N=276)</th>
<th>PL (N=141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>163 (58)</td>
<td>168 (60)</td>
<td>156 (57)</td>
<td>83 (59)</td>
</tr>
<tr>
<td>Women</td>
<td>116 (42)</td>
<td>112 (40)</td>
<td>120 (44)</td>
<td>58 (41)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>56 ± 10</td>
<td>56 ± 9</td>
<td>55 ± 10</td>
<td>55 ± 10</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>93 (33)</td>
<td>102 (36)</td>
<td>91 (33)</td>
<td>45 (32)</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>186 (67)</td>
<td>178 (64)</td>
<td>184 (67)</td>
<td>96 (68)</td>
</tr>
<tr>
<td>American Indian</td>
<td>40 (14)</td>
<td>37 (13)</td>
<td>38 (14)</td>
<td>20 (14)</td>
</tr>
<tr>
<td>Asian</td>
<td>6 (2)</td>
<td>8 (3)</td>
<td>4 (1)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Black</td>
<td>24 (9)</td>
<td>24 (9)</td>
<td>18 (7)</td>
<td>10 (7)</td>
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<tr>
<td>Multiple</td>
<td>3 (1)</td>
<td>3 (1)</td>
<td>3 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Native Hawaiian</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>White</td>
<td>205 (74)</td>
<td>207 (74)</td>
<td>211 (76)</td>
<td>103 (73)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>33 ± 5</td>
<td>33 ± 6</td>
<td>34 ± 5</td>
<td>33 ± 6</td>
</tr>
<tr>
<td>Weight</td>
<td>96 ± 20</td>
<td>96 ± 21</td>
<td>97 ± 19</td>
<td>94 ± 19</td>
</tr>
<tr>
<td>Diabetes Duration (yrs)</td>
<td>9 ± 6</td>
<td>9 ± 5</td>
<td>9 ± 6</td>
<td>9 ± 6</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.1 ± 1.3</td>
<td>8.1 ± 1.2</td>
<td>8.1 ± 1.3</td>
<td>8.1 ± 1.3</td>
</tr>
<tr>
<td>Fasting Plasma Glucose (mg/dL)</td>
<td>162 ± 56</td>
<td>159 ± 50</td>
<td>164 ± 55</td>
<td>166 ± 54</td>
</tr>
<tr>
<td>OAM treatment, n (%)a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 OAM</td>
<td>55 (20)</td>
<td>67 (24)</td>
<td>76 (27)</td>
<td>44 (31)</td>
</tr>
<tr>
<td>2 OAMs</td>
<td>155 (56)</td>
<td>142 (51)</td>
<td>135 (49)</td>
<td>62 (44)</td>
</tr>
<tr>
<td>&gt;2 OAMs</td>
<td>63 (23)</td>
<td>67 (24)</td>
<td>66 (24)</td>
<td>33 (23)</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>127 ± 15</td>
<td>127 ± 15</td>
<td>127 ± 15</td>
<td>125 ± 14</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>81 ± 9</td>
<td>77 ± 10</td>
<td>77 ± 10</td>
<td>77 ± 11</td>
</tr>
</tbody>
</table>

aData at screening

Data are means ± SD or n (%) unless otherwise indicated. Abbreviations: DU = dulaglutide; EX = exenatide; DBP = diastolic blood pressure; HbA1c = glycosylated hemoglobin A1c; OAM = oral antiglycemic medication; PL = placebo; SBP = systolic blood pressure.
Table 2. Safety assessments, change from baseline in vital signs, and treatment emergent dulaglutide anti-drug antibodies

<table>
<thead>
<tr>
<th>Variable</th>
<th>26 weeks</th>
<th>52 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DU 1.5 mg</td>
<td>DU 0.75 mg</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
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<tr>
<td>Serious adverse events, n (%)</td>
<td>12 (4)</td>
<td>15 (5)</td>
</tr>
<tr>
<td>Adverse events, (patients with ≥1 event, n [%])</td>
<td>215 (77)</td>
<td>199 (71)</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>0.11 ± 0.83</td>
<td>-0.36 ± 0.82</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>0.67 ± 0.55</td>
<td>0.56 ± 0.54</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>2.80 ± 0.52</td>
<td>2.80 ± 0.51</td>
</tr>
<tr>
<td>Dulaglutide ADA, n (%)</td>
<td>4 (1.4)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Exenatide ADA, n [%]</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Data are presented as n (%) and LS mean ± SE where applicable. * P < 0.05 vs. exenatide and placebo, respectively. ** P < 0.001 vs. placebo, respectively.

Abbreviations: ADA = dulaglutide anti-drug antibody; bpm = beats per minute; DBP = diastolic blood pressure; DU = dulaglutide; EX = exenatide; GI = gastrointestinal; PL = placebo; pts = patients; SBP = systolic blood pressure; TE = treatment emergent; URI = upper respiratory infection; UTI = urinary tract infection.
Figure 1.

A. 

<table>
<thead>
<tr>
<th>Treatment Period</th>
<th>0</th>
<th>26</th>
<th>52</th>
<th>56</th>
</tr>
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<tbody>
<tr>
<td>Lead In</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomization</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Primary Time Point (Week)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final Time Point</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety Follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

B. 

Randomized and Treated (N=976) 
Discontinued prior to treatment (n=2; Exenatide)

Dulaglutide 1.5 mg (N=279) 
Dulaglutide 0.75 mg (N=280) 
Exenatide (N=273) 
Placebo (N=141)

Discontinued study: 
(n=19) 
Adverse event: 8 
Lack of efficacy: 1 
Lost to follow-up: 1 
Other: 9

Discontinued study: 
(n=17) 
Adverse event: 4 
Lack of efficacy: 0 
Lost to follow-up: 7 
Other: 6

Discontinued study: 
(n=26) 
Adverse event: 9 
Lack of efficacy: 1 
Lost to follow-up: 3 
Other: 13

Discontinued study: 
(n=17) 
Adverse event: 3 
Lack of efficacy: 3 
Lost to follow-up: 5 
Other: 6

Completed 26 weeks: 
(n=260) 
Dulaglutide 1.5 mg (n=263) 
Dulaglutide 0.75 mg (n=282)

Completed 52 Weeks: 
(n=245) 
Dulaglutide 1.5 mg (n=254) 
Dulaglutide 0.75 mg (n=237)

Completed 52 Weeks: 
(n=59) 
Dulaglutide 1.5 mg (n=62) 
Dulaglutide 0.75 mg (n=62)

Discontinued study: 
(n=3) 
Adverse event: 1 
Lost to follow-up: 1 
Other: 1

Completed 52 Weeks: 
(n=62)
Table S1. Other end points of interest, change from baseline to 26 and 52 weeks

<table>
<thead>
<tr>
<th></th>
<th>26 weeks</th>
<th>52 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DU 1.5 mg (N=279)</td>
<td>DU 0.75 mg (N=280)</td>
</tr>
<tr>
<td><strong>Insulin and HOMA Parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting Insulin (pmol/L)</td>
<td>7.3 (4.2)</td>
<td>1.9 (4.3)</td>
</tr>
<tr>
<td>HOMA2-%B</td>
<td>36 (2.6)</td>
<td>24 (2.7)</td>
</tr>
<tr>
<td>HOMA2-%S</td>
<td>-3.1 (2.9)</td>
<td>1.2 (3.0)</td>
</tr>
<tr>
<td><strong>Lipid Parameters, mean ± SD (mmol/L)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>-0.15 ± 0.82**</td>
<td>-0.10 ± 0.85</td>
</tr>
<tr>
<td>LDL</td>
<td>-0.11 ± 0.66*</td>
<td>-0.08 ± 0.73</td>
</tr>
<tr>
<td>HDL</td>
<td>0.04 ± 0.19</td>
<td>0.02 ± 0.19</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-0.20 ± 1.16**</td>
<td>-0.08 ± 0.76</td>
</tr>
<tr>
<td><strong>Pancreatic Enzymes, Median [Q1,Q3] (U/L)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipase</td>
<td>19 [4, 44]***</td>
<td>8 [-11, 36]***</td>
</tr>
<tr>
<td>Total Amylase</td>
<td>7 [-1, 17]***</td>
<td>3 [-4, 11]***</td>
</tr>
<tr>
<td>p-Amylase</td>
<td>4 [0, 11]***</td>
<td>3 [-1, 7]***</td>
</tr>
<tr>
<td><strong>Patients with TE, abnormal, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipase</td>
<td>46 (17)</td>
<td>37 (13)</td>
</tr>
<tr>
<td>Total Amylase</td>
<td>15 (6)</td>
<td>14 (5)</td>
</tr>
<tr>
<td>p-Amylase</td>
<td>24 (9)</td>
<td>17 (6)</td>
</tr>
<tr>
<td><strong>Pancreatic Enzymes, n (%) of patients with ≥3x ULN</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipase</td>
<td>8 (3.0)</td>
<td>6 (2.2)</td>
</tr>
<tr>
<td>p-Amylase</td>
<td>2 (0.8)</td>
<td>1 (0.4)</td>
</tr>
</tbody>
</table>

*aCumulative number (%) of patients with at least one treatment emergent abnormality. **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.