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REVIEW ARTICLE

Efficacy and safety of dulaglutide in the treatment of type 2 diabetes: a comprehensive review of the dulaglutide clinical data focusing on the AWARD phase 3 clinical trial program

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Summary

Dulaglutide (DU) is a once weekly glucagon-like peptide-1 receptor agonist (GLP-1 RA) approved for the treatment of type 2 diabetes mellitus (T2DM). Glycaemic efficacy and safety characteristics of dulaglutide have been assessed in six Phase 3 studies in the AWARD program. The objective of this review article is to summarize these results from the six completed AWARD studies. At the primary endpoint, in five of the six studies, once weekly dulaglutide 1.5 mg was superior to the active comparator [exenatide, insulin glargine (two studies), metformin, and sitagliptin], with a greater proportion of patients reaching glycated hemoglobin A1c (HbA1c) targets of $<$7.0% (53.0 mmol/mol) and $\leq$6.5% (47.5 mmol/mol). Dulaglutide 1.5 mg was non-inferior to liraglutide in AWARD-6. Once weekly dulaglutide 0.75 mg was evaluated in five of these trials and demonstrated superiority to the active comparator in four of five AWARD studies (exenatide, glargine, metformin, and sitagliptin), and non-inferiority to glargine in the AWARD-2 study. Similar to other GLP-1 receptor agonists, treatment with dulaglutide was associated with weight loss or attenuation of weight gain and low rates of hypoglycaemia when used alone or with non-insulin-secretagogue therapy. The most frequently reported adverse events were gastrointestinal, including nausea, vomiting, and diarrhea. The incidence of dulaglutide antidrug antibody formation was 1–2.8% with rare injection site reactions. In conclusion, dulaglutide is an effective treatment for T2DM and has an acceptable tolerability and safety profile. Copyright © 2016 John Wiley & Sons, Ltd.

Keywords dulaglutide; GLP-1 receptor agonist; type 2 Diabetes

Introduction

Type 2 diabetes mellitus (T2DM) is an increasingly common endocrine disorder characterized by progressive loss of beta cell function leading to dysregulation of glucose homeostasis and chronic hyperglycaemia, which is associated with an increased risk of myocardial infarction, stroke, and peripheral arterial disease, as well as chronic kidney disease, neuropathy,

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and retinopathy [1–3]. Controlling hyperglycaemia is pivotal to avoid the comorbidities of T2DM [2,4–6]. Several classes of oral and injectable antihyperglycaemic agents with different mechanisms of actions are currently available for T2DM treatment. However, hypoglycaemia and weight gain are among the limitations of some currently available antihyperglycaemic medications [4,7].

T2DM pathophysiological abnormalities include an impaired incretin effect [3,8–11]. Of particular interest is the incretin hormone glucagon-like peptide-1 (GLP-1), which is released from intestinal L-cells in response to nutrients, and stimulates glucose-dependent insulin secretion [12–14], suppresses glucagon levels [13,14], delays gastric emptying [14,15], and increases satiety [16,17]. GLP-1 also improves beta cell function and studies on experimental animals and islet/beta cells indicate that GLP-1 enhances beta cell proliferation and differentiation and decreases apoptosis [18]. These actions, with the resulting glucose lowering effects, lower risk for hypoglycaemia, and weight loss potential, make GLP-1 receptor agonists (GLP-1 RAs) an attractive T2DM treatment.

Endogenous GLP-1 has a short half-life ($t_{1/2}$ of about 1–2 min) due to rapid proteolysis by dipeptidyl peptidase-4 (DPP-4) [18–20]. The GLP-1 RA class of drugs utilizes DPP-4 resistant moieties of either a modified exendin-4 peptide or human GLP-1 to enable prolonged activation of the GLP-1 receptor [21,22]. Five GLP-1 RAs with half-lives ranging from hours to days have been developed to allow for less frequent dosing; these GLP-1 RAs include exenatide (twice daily and once weekly), liraglutide, lixisenatide, albiglutide, and dulaglutide.

Dulaglutide is a long-acting human GLP-1 RA approved for the treatment of T2DM. In this manuscript, we review the efficacy and safety of dulaglutide, focusing mainly on results from the six completed Phase 3 studies in the AWARD [**A**ssessment of **W**eekly **A**dminist**R**ation of LY2189265 (Dulaglutide) in **D**iabetes] clinical trial program.

Dulaglutide molecule structure (Figure 1)

Dulaglutide is a recombinant protein consisting of two identical, disulphide-linked chains each containing a DPP-4-protected GLP-1(7–37) analogue fused to a modified immunoglobulin G4 (IgG4) Fc fragment via a small peptide linker. The fusion protein maintains the insulinotropic activity of native GLP-1 with decreased clearance, substantially extended plasma half-life, and markedly flat plasma levels with no burst effect, allowing once weekly dosing [22,23]. The dulaglutide GLP-1 analogue is 90% homologous to native human GLP-1 (7–37) and contains three amino acid substitutions (A8G, G22E, and R36G), which optimized its clinical profile, including protection from DPP-4 inactivation (A8G), increased solubility (G22E), and reduction of immunogenicity via substituting a glycine residue for arginine at position 36 (R36G) to remove a potential T-cell epitope. The IgG4 domain was used to reduce complement-dependent and antibody-dependent cell-mediated cytotoxicity; the IgG4 domain was further modified [alanine substitution at two positions (F234A and L235A)], which reduced interaction with high-affinity Fc receptors resulting in significant reduction of cytotoxicity; S228 was mutated to proline (S228P) to eliminate half-antibody formation, and the C-terminal lysine was removed [22,23].

Pharmacokinetic and pharmacodynamic profile of dulaglutide

Initial safety, efficacy, and PK/PD of dulaglutide were assessed in small populations of healthy volunteers and patients with T2DM in two multiple-dose Phase 1 studies [24,25]. Meta-analyses of Phase 1 data and population pharmacokinetic (PK) modeling indicate that dulaglutide has a half-life of 4.7 days, making it suitable for once weekly administration [26]. Steady state concentrations are reached between 2 and 4 weeks, and the median time to maximum concentration (C_{max}) at steady state is 48 h (mean peak $C_{max} = 114$ ng/mL). Intravenous administration of dulaglutide results in a mean volume of distribution of 5.32 L, indicating dulaglutide is principally distributed in

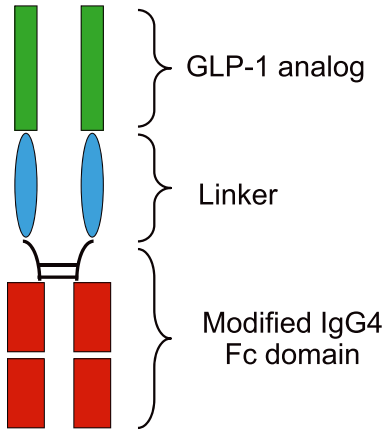

Figure 1. Structure of dulaglutide. Dulaglutide: a recombinant protein with two identical, disulphide-linked chains containing a DPP-4-protected GLP-1(7–37) analogue fused to a modified immunoglobulin G4 (IgG4) Fc fragment via a small peptide linker with a half-life of 4.7 days

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the blood volume. No significant changes in exposure are found based on injection into the abdomen, upper arm, or thigh, and no dose adjustment are required based on body weight, sex, age, or race/ethnicity. In patients with varying degrees of renal or hepatic impairment, no relevant change in dulaglutide exposure was observed relative to the degree of renal or hepatic impairment [27]. Dulaglutide is presumed to be degraded into peptides and amino acids by general protein catabolism mechanisms [26,28].

Dulaglutide phase 2 studies

Dulaglutide was subsequently assessed in two global Phase 2 studies [29,30] and a Phase 2 study in Japanese patients [31] (Supplementary Table 1). Additionally, effects of dulaglutide on blood pressure (BP) and heart rate (HR) in patients with T2DM were examined in a comprehensive Phase 2 ambulatory blood pressure monitoring (ABPM) safety study [32]. At week 16, dulaglutide 0.75 mg was non-inferior to placebo for changes in 24-hour systolic BP (SBP) and dulaglutide 1.5 mg significantly reduced SBP [LS mean difference (95% CI), −2.8 mmHg (−4.6,−1.0); $p \leq 0.001$ for dulaglutide 1.5 mg], while no changes in diastolic BP were noted for either dose. Dulaglutide 0.75 mg was non-inferior to placebo for 24-hour HR [1.6 bpm; (0.3, 2.9); non-inferiority margin of 3 bpm, non-inferiority $p \leq 0.02$], while dulaglutide 1.5 mg had an increase in HR compared with placebo [2.8 bpm (1.5, 4.2), not achieving non-inferiority, non-inferiority *p*-value was not significant].

Dulaglutide phase 3 studies

Dulaglutide phase 3 clinical study design

The dulaglutide Phase 3 clinical trial program was designed to assess the safety and efficacy of dulaglutide in patients with T2DM compared with metformin and as a combination therapy *versus* common second line therapies (sitagliptin, exenatide, liraglutide, and glargine) (Table 1). Dulaglutide was assessed in a broad population of patients across different stages of the T2DM treatment continuum ranging from monotherapy (AWARD-3), combination with one oral antihyperglycaemic medication (OAM) (metformin, in AWARD-5, and AWARD-6), two OAMs [metformin and pioglitazone in AWARD-1 and metformin and sulphonylurea (SU) in AWARD-2], and combination with insulin lispro, with or without metformin (AWARD-4). Treatment periods ranged from 26 weeks to 104 weeks of controlled data, with primary endpoints at either week 26 or 52. AWARD-1 and AWARD-5 included 26-week placebo comparisons, after which, patients randomized to placebo were converted to active therapy to maintain study blind and collect long-term, controlled safety data across the treatment groups. In general, the AWARD clinical program included patients 18 years or older with T2DM, HbA1c ranging from 6.5 to 11.0% (47.5 to 96.7 mmol/mol), and a BMI of ≤45 kg/m^2. Patients were generally excluded if previously prescribed GLP-1 RAs within a certain period prior to participation, had increased serum calcitonin, a history of pancreatitis, or recent cardiovascular events.

The dulaglutide 1.5 mg and 0.75 mg doses studied were chosen based on the results from the dose finding portion of AWARD-5 [33]. Randomizations were stratified by factors that might impact treatment effects (e.g. country, baseline HbA1c, or background medication use). In AWARD-1 to−5, analyses of the primary efficacy measure of change in HbA1c from baseline examined the hypotheses [superiority of both dulaglutide doses (1.5 mg and 0.75 mg) to placebo and/or non-inferiority/superiority of both dulaglutide doses to active comparator] at the primary and final endpoints using gatekeeping strategies to control the type 1 error rate at each time point, as applicable [34–38]. In AWARD-1 to−4 and−6, the prespecified non-inferiority margin was 0.4% [34–36,38,39]. In AWARD-5, the non-

Table 1. Dulaglutide clinical trial program for data analysis

Study	Primary objective	Comparator(s) (dose)	Background medications	ITT population
AWARD-1	ΔHbA1c 26 weeks	Exenatide (10 μg BID) Placebo (to week 26)	Pioglitazone (≥30 mg) Metformin (≥1500 mg)	*N* = 976
AWARD-2	ΔHbA1c 52 weeks	Insulin Glargine (titrated to target)	Glimepiride (≥4 mg) Metformin (≥1500 mg)	*N* = 807
AWARD-3	ΔHbA1c 26 weeks	Metformin (1500–2000 mg QD)	None	*N* = 807
AWARD-4	ΔHbA1c 26 weeks	Insulin Glargine (titrated to target)	Insulin Lispro (titrated to target) ± Metformin (≥1500 mg)	*N* = 884
AWARD-5	ΔHbA1c 52 weeks	Sitagliptin (100 mg QD) Placebo (to week 26)	Metformin (≥1500 mg)	*N* = 1098[a]
AWARD-6	ΔHbA1c 26 weeks	Liraglutide (1.8 mg QD)	Metformin (≥1500 mg)	*N* = 599

[a]Additional 104 patients were discontinued because the treatment dose was not selected for further study.

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inferiority margin was prespecified at 0.25% [40]. AWARD-6 examined the hypothesis of non-inferiority of dulaglutide 1.5 mg to liraglutide 1.8 mg at the week 26 primary endpoint; the primary efficacy measure was change in HbA1c from baseline [39]. Results from the analyses of AWARD-1 to−5 using gatekeeping were summarized using multiplicity-adjusted one-sided *p*-values. Additional efficacy measures included changes in HbA1c over time, percentage of patients achieving an HbA1c of <7.0% (53.0 mmol/mol) and ≤6.5% (47.5 mmol/mol), change in body weight, change in fasting blood glucose (FBG) concentration (plasma or serum were used by a central lab depending on study), and self-monitored blood glucose (SMPG) measures (glucose meters displayed measurements corresponding to plasma glucose concentrations).

Incidence of TEAEs, SAEs, and deaths were collected along with the rate and reason for discontinuations. Special safety issues included GI tolerability, pancreatic safety, immunogenicity, systemic hypersensitivity reactions, thyroid safety, hypoglycaemia, and cardiovascular safety. Cardiovascular events, all deaths, and possible pancreatitis events were adjudicated by independent, blinded Clinical Event Classification (CEC) committees.

Efficacy of dulaglutide in phase 3 trials

Different studies included patients at different stages of T2DM, the mean duration of diabetes ranged from 2.6 to 12.7 years and mean baseline HbA1c ranged from 7.6% to 8.5% (59.6 mmol/mol to 69.4 mmol/mol; Supplementary Table 2). However, in each Phase 3 study, baseline characteristics were balanced across arms.

Dulaglutide Efficacy Compared with Oral Agents (metformin in AWARD-3 and sitagliptin in AWARD-5)

In the dulaglutide Phase 3 program, two direct head-to-head studies comparing dulaglutide to oral agents have been completed. In AWARD-3, dulaglutide (1.5 mg and 0.75 mg) was compared with metformin monotherapy [34]. In AWARD-5, dulaglutide (1.5 mg and 0.75 mg) was compared with sitagliptin added onto metformin [40].

Effect on HbA1c

Monotherapy with dulaglutide 1.5 mg and 0.75 mg, administered alone, resulted in superior HbA1c reductions at week 26 compared with metformin (Figures 2 and 3, Supplementary Table 3). At the final week 52 endpoint, dulaglutide 1.5 mg was superior, and dulaglutide 0.75 mg non-inferior, to metformin on change in HbA1c from baseline (Table 2) [34]. At week 26, significantly greater proportions of patients reached an HbA1c target of <7.0% (53.0 mmol/mol) and ≤6.5% (47.5 mmol/mol) with dulaglutide 1.5 mg and 0.75 mg compared with metformin. However, at week 52, only dulaglutide 1.5 mg had significantly more patients reaching both glycaemic targets [34] (Table 2, Supplementary Table 3).

AWARD-5 included a 26-week placebo-controlled period in which dulaglutide (1.5 mg and 0.75 mg) was superior to placebo for HbA1c reduction ($p < 0.001$). Both dulaglutide doses demonstrated superiority in HbA1c reduction to sitagliptin (all with background metformin)

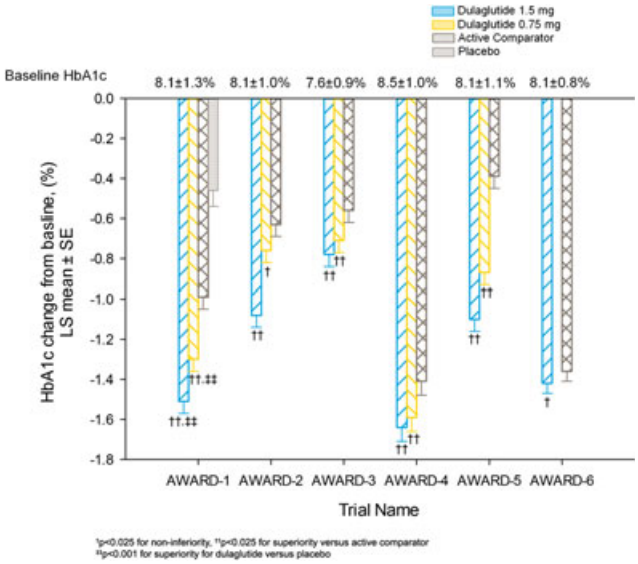

Figure 2. HbA1c change from baseline at primary endpoint. The $^{\dagger}p < 0.025$ for non-inferiority, $^{\dagger\dagger}p < 0.025$ for superiority versus active comparator $^{\ddagger\ddagger}p < 0.001$ for superiority for dulaglutide *versus* placebo

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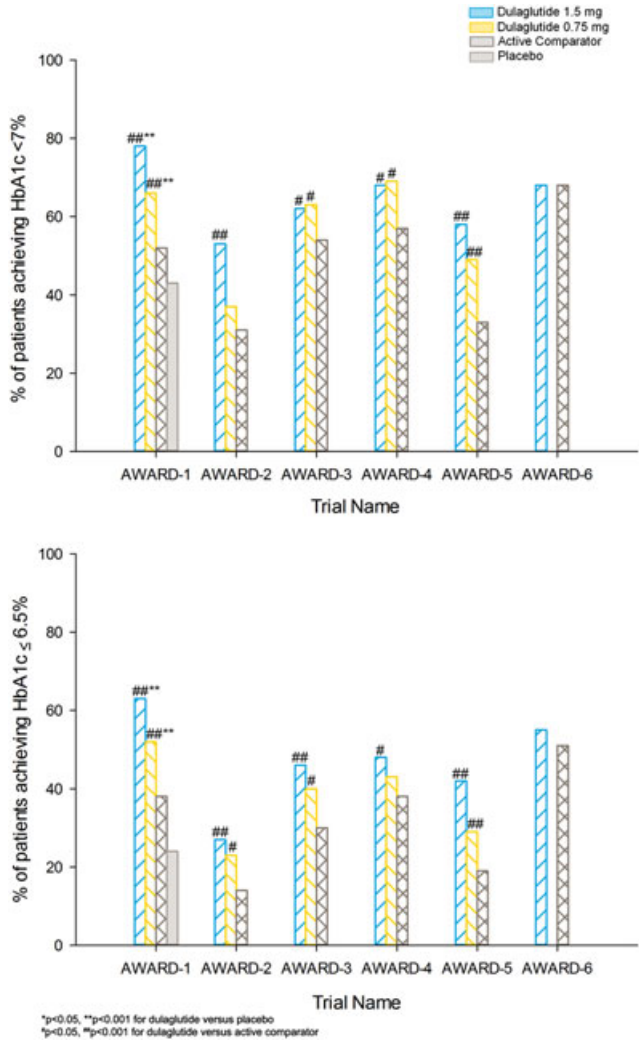

Figure 3. Percentage of patients achieving HbA1c goal at primary endpoint. The *$p < 0.05$, **$p < 0.001$ for dulaglutide *versus* placebo $^{\#}p < 0.05$, $^{\#\#}p < 0.001$ for dulaglutide *versus* active comparator

at week 52 and the effect was persistent to week 104 (Figure 2, Supplementary Table 3). Significantly greater proportions of patients receiving dulaglutide 1.5 mg and 0.75 mg achieved an HbA1c target of <7.0% (53.0 mmol/mol) and ≤6.5% (47.5 mmol/mol), respectively, compared with sitagliptin [37,40] (Table 2, Figure 3, Supplementary Table 3).

Effect on blood glucose

Monotherapy with dulaglutide 1.5 mg resulted in greater FBG reductions compared with metformin at week 52 (AWARD-3; Table 2). Patients in both dulaglutide groups and the metformin treatment group experienced similar reductions in postprandial glucose (PPG) at weeks 26 and 52 as indicated by change in PPG over time (data not shown) [34]. In combination with metformin, decreases in FBG occurred within 2 weeks of initiation and were stable thereafter. Both dulaglutide 1.5 mg and 0.75 mg significantly reduced FBG from baseline compared with sitagliptin at the primary and final endpoints (AWARD-5; Table 2, Supplementary Table 3). Self-monitored glucose data, including PPG levels, were not collected in AWARD-5 [37,40].

Effect on body weight

In the monotherapy study, weight loss was similar between dulaglutide 1.5 mg and metformin (Table 2, Figure 4, Supplementary Table 3). Dulaglutide 0.75 mg demonstrated significantly less weight loss than metformin [34]. Compared with sitagliptin, weight loss

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Table 2. Summary of clinical efficacy at final endpoint

Study/ study treatment LSM (SE)	*N*	ΔHbA1c (%)	ΔHbA1c (mmol/mol)	ΔFBG (mmol/L)	% Patients reaching glycaemic goal HbA1c <7.0% (53.0 mmol/mol)	% Patients reaching glycaemic goal HbA1c ≤6.5% (47.5 mmol/mol)	Change in body weight (kg)
AWARD-1 (dulaglutide vs. exenatide BID; background pioglitazone and metformin) [week 52 final endpoint]							
Dulaglutide 1.5 mg	279	−1.36 (0.08)††	−14.9 (0.9)††	−2.1 (0.2)##	71##	57##	−1.1 (0.4)
Dulaglutide 0.75 mg	280	−1.07 (0.08)††	−11.7 (0.9)††	−1.6 (0.2)#	59#	48##	0.4 (0.4)#
Exenatide	276	−0.80 (0.08)	−8.8 (0.9)	−1.1 (0.2)	49	35	−0.8 (0.4)
AWARD-2 (dulaglutide vs. insulin glargine; background glimepiride and metformin) [week 78 final endpoint]							
Dulaglutide 1.5 mg	273	−0.90 (0.07)††	−9.8 (0.8)††	−1.1 (0.2)#	49##	28##	−2.0 (0.3)##
Dulaglutide 0.75 mg	272	−0.62 (0.07)†	−6.8 (0.8)†	−0.6 (0.2)##	34	22	−1.5 (0.3)##
Insulin Glargine	262	−0.59 (0.07)	−6.5 (0.8)	−1.6 (0.2)	31	17	1.3 (0.3)
AWARD-3 (dulaglutide monotherapy vs. metformin) [week 52 final endpoint]							
Dulaglutide 1.5 mg	269	−0.70 (0.07)††	−7.7 (0.8)††	−1.6 (0.2)#	60#	42##	−1.9 (0.3)
Dulaglutide 0.75 mg	270	−0.55 (0.07)†	−6.0 (0.8)†	−1.0 (0.2)	53	35	−1.1 (0.3)#
Metformin	268	−0.51 (0.07)	−5.6 (0.8)	−1.2 (0.2)	48	28	−2.2 (0.3)
AWARD-4 (dulaglutide vs. insulin glargine; background insulin lispro ± metformin) [week 52 final endpoint]							
Dulaglutide 1.5 mg	295	−1.48 (0.08)††	−16.2 (0.9)††	0.1 (0.2)##	59#	37	−0.4(0.3)##
Dulaglutide 0.75 mg	293	−1.42 (0.08)††	−15.5 (0.9)††	0.4 (0.2)##	56	35	0.9 (0.3)##
Insulin Glargine	296	−1.23 (0.08)	−13.5 (0.9)	−1.0 (0.2)	49	30	2.9 (0.3)
AWARD−5 (dulaglutide vs. sitagliptin) [week 104 final endpoint]							
Dulaglutide 1.5 mg	304	−0.99 (0.06)††	−10.8 (0.7)††	−2.0 (0.2)††	54##	39##	−2.9 (0.3)##
Dulaglutide 0.75 mg	302	−0.71 (0.07)††	−7.8 (0.8)††	−1.4 (0.2)††	45##	24##	−2.4 (0.3)
Sitagliptin	315	−0.32 (0.06)	−3.5 (0.7)	−0.5 (0.2)	31	14	−1.8 (0.3)

Abbreviations: BID = twice daily; FBG = fasting blood glucose; LOCF = last observation carried forward; LS = least squares; MMRM = mixed-effect model repeated measure; SE = standard error;
Analysis methods: change in HbA1c and weight, ANCOVA (LOCF); percentage patients achieving HbA1c target, logistic regression (LOCF); change in plasma glucose, MMRM.
†Multiplicity adjusted 1-sided $p < 0.025$ for non-inferiority (no adjustment for AWARD-6),
††multiplicity adjusted 1-sided $p < 0.025$ for superiority, versus active comparator for HbA1c only.
††††multiplicity adjusted 1-sided $p < 0.001$ for superiority for dulaglutide versus placebo for HbA1c only.
*$p < 0.05$,
**$p < 0.001$ for dulaglutide or active comparator *versus* placebo.
#$p < 0.05$,
##$p < 0.001$ for dulaglutide *versus* active comparator.

was significantly greater with dulaglutide 1.5 mg at week 52 and 104, and dulaglutide 0.75 mg at week 52 (Table 2, Figure 4, Supplementary Table 3) [37,40].

Dulaglutide Efficacy Compared with Insulin Glargine (AWARD-2 and AWARD-4)

In the dulaglutide Phase 3 program, two direct head-to-head glargine comparison studies have been completed. In AWARD-2, dulaglutide (1.5 mg and 0.75 mg) was compared with glargine added onto glimepiride and metformin [38]. In AWARD-4, dulaglutide (1.5 mg and 0.75 mg) was compared with glargine added onto lispro with or without metformin [36].

Effect on HbA1c

When compared with insulin glargine, all in combination with maximally tolerated doses of metformin and glimepiride in AWARD-2, dulaglutide 1.5 mg was superior, and dulaglutide 0.75 mg non-inferior, to insulin glargine for HbA1c reduction following 52 and 78 weeks of therapy (Table 2, Figures 2 and 3, Supplementary Table 3) [38]. In AWARD-4, in patients receiving concomitant prandial insulin lispro with or without metformin, at week 26 and 52, both dulaglutide doses were superior to insulin glargine, for HbA1c change from baseline (Table 2, Figures 2 and 3, Supplementary Table 3) [36].

At the primary endpoints in both trials, significantly greater proportion of patients receiving dulaglutide 1.5 mg achieved an HbA1c target of <7.0% (53.0 mmol/mol) and ≤6.5% (47.5 mmol/mol) compared with insulin glargine (Figure 3, Supplementary Table 3). At week 78 in AWARD-2, significantly greater proportions of patients receiving dulaglutide 1.5 mg achieved both HbA1c targets compared with insulin glargine (Table 2) [38]. At the week 52 final endpoint of AWARD-4, significantly greater proportions of patients receiving dulaglutide 1.5 mg achieved an HbA1c of <7.0% (53.0 mmol/mol) (Table 2) [36].

Effect on blood glucose

At week 52 in AWARD-2, the decrease from baseline in FBG was greater for glargine than dulaglutide 0.75 mg,

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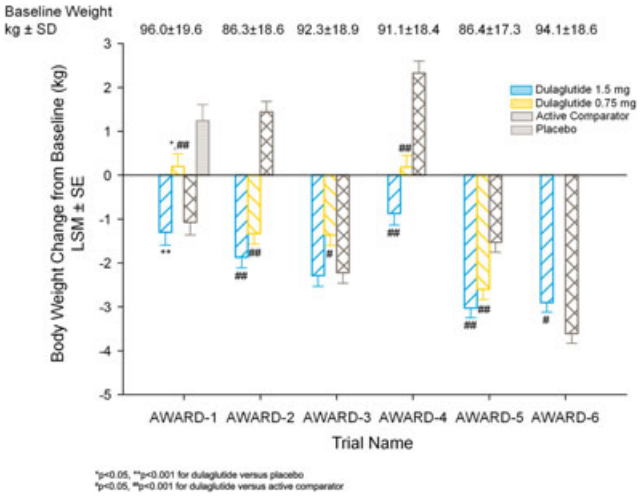

Figure 4. Body weight change from baseline at primary endpoint. The *$p < 0.05$, **$p < 0.001$ for dulaglutide *versus* placebo $^{\#}p < 0.05$, $^{\#\#}p < 0.001$ for dulaglutide *versus* active comparator

and no differences between dulaglutide 1.5 mg and glargine were noted (Supplementary Table 3). The maximal reduction in mean FBG was achieved by 2 weeks for both dulaglutide doses [38]. At week 78, treatment with glargine resulted in a greater decrease in FBG than either dulaglutide group (Table 2) [38].

With respect to SMPG profiles, at week 52 in AWARD-2, the decrease from baseline for 2-hour PPG was similar after morning and midday meals, and greater after the evening meal with dulaglutide 1.5 mg as compared with glargine ($p < 0.05$), resulting in a greater decrease in overall daily mean PPG for dulaglutide 1.5 mg [38]. Lower pre-dinner and bedtime glucose values were observed with dulaglutide 1.5 mg as compared with glargine ($p < 0.05$) [38].

In AWARD-4, the reductions from baseline in FBG at weeks 26 and 52 were significantly greater with glargine *versus* either dulaglutide dose (Table 2, Supplementary Table 3). For SMPG, the reductions in mean fasting/pre-meal PG were significantly greater with glargine, while the decrease in mean PPG was significantly greater with dulaglutide 1.5 mg [36]. At week 26, reductions in PPG were significantly greater with both dulaglutide doses *versus* glargine at the 2-hour post midday meal, 2-hour post-evening meal, and bedtime ($p < 0.05$, all) [36]. Reductions in PPG with glargine after the morning meal were similar to dulaglutide 1.5 mg, but significantly greater than dulaglutide 0.75 mg ($p < 0.05$).

Effect on body weight

In patients receiving background glimepiride and metformin (AWARD-2), patients in the dulaglutide treatment groups exhibited body weight loss, while those in the glargine group gained weight, and the differences between dulaglutide treatment arms and glargine were significant (Table 2, Supplementary Table 3) [38]. In patients receiving background insulin lispro with or without metformin (AWARD-4), dulaglutide doses demonstrated either weight loss or significantly less weight gain compared with glargine at the primary and final endpoints (Table 2, Supplementary Table 3) [36].

Dulaglutide Efficacy Compared with Other GLP-1 RAs

In the dulaglutide Phase 3 program, two direct head-to-head GLP-1 RA comparison studies have been completed. In AWARD-1, dulaglutide (1.5 mg and 0.75 mg) was compared with twice-daily exenatide added onto pioglitazone and metformin [35]. In AWARD-6, dulaglutide 1.5 mg was compared with once daily liraglutide 1.8 mg added onto metformin [39].

Effect on HbA1c

Both dulaglutide 1.5 mg and 0.75 mg were superior to placebo at week 26 and exenatide twice daily at weeks 26 and 52 (Table 2, Figure 2, Supplementary Table 3) [35]. Once weekly dulaglutide 1.5 mg was non-inferior to once daily liraglutide 1.8 mg at the week 26 study endpoint (Figure 2, Supplementary Table 3) [39]. When compared with exenatide for percentage of patients achieving HbA1c targets of <7.0% (53.0 mmol/mol) and ≤6.5% (47.5 mmol/mol), both dulaglutide doses had a greater percentage of patients achieving both targets *versus* exenatide at weeks 26 and 52 (Table 2, Figure 3, Supplementary Table 3) [35]. A similar percentage of patients achieved

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both HbA1c targets in the liraglutide and dulaglutide treatment groups (Figure 3, Supplementary Table 3) [39].

Effect on blood glucose

In AWARD-1, the maximal reduction in mean FBG was achieved within 2 weeks for both dulaglutide doses [35]. The decrease in FBG was significantly larger for both dulaglutide doses compared with placebo at week 26 and exenatide at weeks 26 and 52 (Table 2, Supplementary Table 3) [35]. Dulaglutide 1.5 mg and liraglutide 1.8 mg demonstrated similar FBG reductions from baseline at week 26 (Supplementary Table 3) [39].

Dulaglutide 1.5 mg and 0.75 mg were associated with greater reduction in the mean of all premeal PG compared with placebo and exenatide ($p < 0.05$, both comparisons) [35]. Patients receiving dulaglutide 1.5 mg had a significantly greater reduction in the mean of all PPG values compared with exenatide ($p = 0.047$). Reductions in the mean of all 2-h PPG excursions in the exenatide group was significantly greater than in the dulaglutide groups ($p < 0.001$, both comparisons) [35]. The SMPG profile at week 26 was similar for dulaglutide 1.5 mg and liraglutide 1.8 mg in AWARD-6 [39].

Effects on body weight

Dulaglutide 1.5 mg and exenatide exhibited similar effects on body weight reduction (Table 2, Figure 4, Supplementary Table 3), both demonstrating significant weight reduction *versus* placebo. Patients receiving dulaglutide 0.75 mg experienced a small (<1 kg), but statistically significant, weight gain at both endpoints compared with exenatide [35]. In AWARD-6, while both treatment groups experienced significant weight reductions, patients taking dulaglutide 1.5 mg demonstrated significantly less weight loss compared with liraglutide, with a treatment difference of 0.7 kg (Figure 4 , Supplementary Table 3) [39].

Dulaglutide safety in phase 3 trials

Deaths and SAEs

There were 15 deaths in the six Phase 3 studies (four dulaglutide 1.5 mg, three dulaglutide 0.75 mg, five glargine, and three sitagliptin) [35–38,40]. The majority of deaths were cardiovascular in nature. The incidence of SAEs was generally similar between dulaglutide and active comparators; significantly fewer SAEs were reported with dulaglutide 1.5 mg *versus* insulin glargine in AWARD-4 (Table 3), mainly driven by the higher number of severe hypoglycaemia events reported in the glargine group [36].

Treatment-emergent adverse events (TEAEs) and gastrointestinal adverse events (AEs)

The clinical safety profile of dulaglutide was generally similar to other GLP-1 RAs. The most common AEs associated with dulaglutide were gastrointestinal (GI) in nature; most commonly nausea, diarrhea, and vomiting (Table 3), as well as decreased appetite and dyspepsia. The incidence of these GI AEs in dulaglutide 1.5 mg was similar to other GLP-1 RAs in direct head-to-head comparisons to exenatide and liraglutide [35,39], and lower for patients receiving dulaglutide 0.75 mg compared with exenatide [35] (Table 3). The majority of GI events were mild to moderate in severity. The incidence of nausea peaked at 1–2 weeks and decreased thereafter [35,38,39].

Discontinuations due to AEs were generally low (1% to 11%), with the exception of AWARD-5 (21%), which required discontinuation of patients who developed severe, persistent hyperglycaemia (Table 3). Treatment discontinuations due to AEs were similar between dulaglutide and comparators (Table 3). Nausea was the most common AE leading to discontinuation. In the head-to-head comparison studies, the incidence of discontinuations due to nausea was similar between dulaglutide 1.5 mg and exenatide in AWARD-1 (three patients and four patients) [35], and dulaglutide 1.5 mg and liraglutide 1.8 mg in AWARD-6 (five patients in each group) [39].

Hypoglycaemia

In AWARD studies, total hypoglycaemia was defined as plasma glucose ≤3.9 mmol/L (≤70 mg/dL) and/or symptoms and/or signs attributable to hypoglycaemia. Severe hypoglycaemia was defined as any episode requiring the assistance of another person to actively administer therapy according to the investigator. The rates of total hypoglycaemia in dulaglutide arms were relatively low and were comparable with metformin, sitagliptin, exenatide, and liraglutide (Table 4) [34,35,37,39,40]. In AWARD-1, two events of severe hypoglycaemia occurred in exenatide-treated patients, and no severe hypoglycaemia was reported in AWARD-3, AWARD-5 or AWARD-6 (Table 4) [34,35,37,39,40].

Rates of hypoglycaemia were higher in all treatment arms with the concomitant use of high dose glimepiride or insulin lispro (in AWARD-2 and AWARD-4, respectively)

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Table 3. Summary of serious AEs, treatment-emergent AEs, GI events, and discontinuations due to AEs

n (%) of patients report events; by study treatment	SAEs	Patients with ≥1 TEAE	Nausea	Vomiting	Diarrhea	Discontinuations due to AE
AWARD-1 (dulaglutide vs. exenatide BID; background pioglitazone and metformin) [week 52 final endpoint]						
Dulaglutide 1.5 mg	18 (7)	226 (81)	81 (29)	47 (17)	36 (13)	9 (3)
Dulaglutide 0.75 mg	22 (8)	220 (79)	47 (17)#	17 (6)#	26 (9)	4 (1)
Exenatide BID	27 (10)	221 (80)	77 (28)	33 (12)	21 (8)	10 (4)
AWARD-2 (dulaglutide vs. insulin glargine; background glimepiride and metformin) [week 78 final endpoint]						
Dulaglutide 1.5 mg	32 (12)	201 (74)	42 (15)##	18 (6.6)#	29 (11)	9 (3)
Dulaglutide 0.75 mg	28 (10)	188 (69)	21 (8)##	10 (3.7)	25 (9)	8 (3)
Insulin glargine	32 (12)	192 (73)	4 (2)	3 (1.1)	15 (6)	5 (2)
AWARD-3 (dulaglutide monotherapy vs. metformin) [week 52 final endpoint]						
Dulaglutide 1.5 mg	15 (6)	179 (67)	53 (20)	26 (9.7)	30 (11)	14 (5)
Dulaglutide 0.75 mg	20 (7)	177 (66)	31 (12)	20 (7.4)	21 (8)	8 (3)
Metformin	16 (6)	170 (63)	43 (16)	13 (4.9)	37 (14)	12 (5)
AWARD-4 (dulaglutide vs. insulin glargine; background insulin lispro ± metformin) [week 52 final endpoint]						
Dulaglutide 1.5 mg	27 (9)#	217 (74)	76 (26)##	36 (12.2)##	49 (17)##	31 (11)[a]
Dulaglutide 0.75 mg	44 (15)	230 (78)##	52 (18)##	31 (10.6)##	46 (16)##	21 (7)[a]
Insulin glargine	54 (18)	206 (70)	10 (3)	5 (1.7)	18 (6)	9 (3)[a]
AWARD-5 (dulaglutide vs. sitagliptin) [week 104 final endpoint][a]						
Dulaglutide 1.5 mg	36 (12)	259 (85)#	53 (17)#	41 (14)#	49 (16)#	63 (21)[b]
Dulaglutide 0.75 mg	23 (8)	255 (84)#	44 (15)#	25 (8)#	36 (12)#	64 (21)[b]
Sitagliptin	32 (10)	242 (77)	21 (7)	11 (4)	18 (6)	65 (21)[b]
AWARD-6 (dulaglutide 1.5 mg vs. liraglutide; background metformin) [week 26 primary/final endpoint]						
Dulaglutide 1.5 mg	5 (2)	185 (62)	61 (20)	21 (7)	36 (12)	18 (6)[a]
Liraglutide	11 (4)	189 (63)	54 (18)	25 (8)	36 (12)	18 (6)[a]

[a]Includes patients who stopped study drug but remained in the study as well as those who withdrew from the study.
[b]During the treatment period, patients who developed persistent or worsening hyperglycaemia based on pre-specified thresholds were discontinued, and this was recorded as an adverse event of hyperglycaemia [37].
Abbreviations: AE = adverse event; BID = twice daily; SAE = serious adverse event; TEAE = treatment emergent adverse event.
#$p < 0.05$,
##$p < 0.001$ for dulaglutide *versus* active comparator.

(Table 4). Notably, in the setting of concomitant metformin plus glimepiride in AWARD-2, the rate of total hypoglycaemia was significantly lower for both dulaglutide 1.5 mg and 0.75 mg through week 78 compared with insulin glargine (Table 4). Also, nocturnal hypoglycaemia was more frequently observed with insulin glargine than in either dulaglutide group ($p < 0.001$, both) [38]. A total of four patients experienced severe hypoglycaemia: two patients in the insulin glargine group while on concomitant glimepiride, and two in the dulaglutide 1.5 mg group with one patient on concomitant glimepiride [38].

In AWARD-4, where dulaglutide or glargine was used in combination with titrated prandial insulin lispro (with or without metformin), the rate of total hypoglycaemia for dulaglutide 1.5 mg was significantly lower than insulin glargine (Table 4). The incidence of nocturnal hypoglycaemia was also lower in the dulaglutide groups ($p \leq 0.001$) [36]. Reports of severe hypoglycaemia were numerically higher in the glargine group (Table 4) [36].

Pancreatic and thyroid safety

In the AWARD Phase 3 program, seven events of adjudicated pancreatitis were reported across treatment groups. In AWARD-5, three events of pancreatitis were confirmed [two in sitagliptin and one in placebo/sitagliptin group (during the sitagliptin period)] [40]. In AWARD-2, three cases of pancreatitis (two acute, one chronic) were confirmed in dulaglutide-treated patients (one dulaglutide 0.75 mg and two in dulaglutide 1.5 mg). One of the acute cases was reported one day post-treatment with dulaglutide 0.75 mg in an asymptomatic patient, with a workup performed based on abnormal lab values prior to treatment [38]. In AWARD-1, one patient had adjudicated chronic pancreatitis in the dulaglutide 1.5 mg group [35]. No cases of adjudicated pancreatitis were reported in AWARD-3, AWARD-4, or AWARD-6 [34,36,39]. Within the Phase 2 program, two additional events of pancreatitis (one placebo, one dulaglutide 1.0 mg) were positively adjudicated [29,30,41]. In the AWARD studies, one patient reported a pancreatic carcinoma in the dulaglutide 1.5 mg treatment group within AWARD-1.

In the AWARD program, serial laboratory assessments of pancreatic amylase (p-amylase), total amylase, and lipase, were performed. Confirmed enzyme elevations and suspected pancreatitis cases were adjudicated by an independent Clinical Event Classification committee. In all Phase 2 and 3 studies, patients exposed to dulaglutide had mean increases from baseline in lipase and/or p-amylase of 14–20%, while placebo-treated patients

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Table 4. Summary of hypoglycaemia (total and severe)

Hypoglycaemia by Treatment	Total hypoglycaemia[a] Incidence (%)	Total hypoglycaemia[a] 1-year adjusted rate (mean events/patient/year)	Severe hypoglycaemia[b] Events (patients)
AWARD-1 (dulaglutide vs. exenatide BID; background pioglitazone and metformin)[week 26 primary endpoint]			
Dulaglutide 1.5 mg	10.4#	0.45	0
Dulaglutide 0.75 mg	10.7	1.10	0
Exenatide BID	15.9	1.47	2 (2)
AWARD-2 (dulaglutide vs. insulin glargine; background glimepiride and metformin) [through week 78 final endpoint]			
Dulaglutide 1.5 mg	58.6#	4.31##	2 (2)
Dulaglutide 0.75 mg	56.6##	4.18##	0
Insulin Glargine	71.4	6.92	2 (2)
AWARD-3 (dulaglutide monotherapy vs. metformin) [week 52 final endpoint]			
Dulaglutide 1.5 mg	12.3	0.89	0
Dulaglutide 0.75 mg	11.1	0.47	0
Metformin	12.7	0.29	0
AWARD-4 (dulaglutide vs. insulin glargine; background insulin lispro ± metformin) [week 52 final endpoint]			
Dulaglutide 1.5 mg	86.6	41.52##	11 (10)
Dulaglutide 0.75 mg	90.1	47.42	15 (7)
Insulin Glargine	90.2	55.93	22 (15)
AWARD-5 (dulaglutide vs. sitagliptin; background metformin) [week 104 final endpoint]			
Dulaglutide 1.5 mg	12.8	0.3	0
Dulaglutide 0.75 mg	8.6	0.2	0
Sitagliptin	8.6	0.2	0
AWARD-6 (dulaglutide 1.5 mg vs. liraglutide; background metformin) [week 26 primary/final endpoint]			
Dulaglutide 1.5 mg	9	0.34	0
Liraglutide	6	0.52	0

[a]Total hypoglycaemia was defined as plasma glucose (PG) ≤3.9 mmol/L and/or symptoms and/or signs attributable to hypoglycaemia.
[b]Severe hypoglycaemia was defined as an episode requiring the assistance of another person to actively administer therapy as determined by the investigator.
Abbreviations: BID = twice daily.
#$p < 0.05$,
##$p < 0.001$ for dulaglutide *versus* active comparator.

had mean increases of up to 3% [28]. Among the active comparators, increases in pancreatic enzymes were also noted with metformin, sitagliptin, exenatide, and liraglutide [34,35,37,39,40]. These elevations observed during routine serial assessments occurred in the absence of other symptoms and were not predictive of acute pancreatitis. In the GLP-1 RA comparator studies, the observed increase in amylase was greater for dulaglutide 1.5 mg compared with exenatide at the final endpoint in AWARD-1, and was comparable with liraglutide at the week 26 final endpoint for AWARD-6 [35,39]. At the final endpoint, increases in lipase levels were not significantly different between dulaglutide and exenatide [35], but significantly smaller increases were observed in dulaglutide 1.5 mg compared with liraglutide [39].

For thyroid safety, in AWARD-5, one report of medullary thyroid carcinoma (MTC) was reported in a patient who received dulaglutide 2.0 mg for approximately 6 months in the dose-finding stage of AWARD-5 [33]. This cancer was determined to be pre-existing [retrospectively analyzed baseline calcitonin level was significantly elevated, nearly eight times the upper limit normal (ULN), prior to receiving study drug]. Limited data from this patient also suggests no increased stimulation of calcitonin was evident following 6 months of dulaglutide exposure. Serum calcitonin was measured throughout the studies to monitor for potential MTC cases. In response to treatment with dulaglutide, mean calcitonin values did not change during any of the AWARD studies.

Cardiovascular (CV) safety

Definitive effects of dulaglutide on BP and HR were determined in the ABPM study: Dulaglutide 1.5 mg demonstrated a decrease in SBP (mean 2.8 mmHg), with no changes in DBP, and an increase in HR of 2–4 bpm compared with placebo. The AWARD studies generally demonstrated consistent results with the ABPM study [28]. Dulaglutide registration information from completed Phase 2 and Phase 3 studies (AWARD-6 not included) indicates that a mean increase from baseline in PR interval of 2–3 milliseconds was observed in dulaglutide-treated patients compared with a decrease of 0.9 milliseconds in placebo-treated patients. Generally, dulaglutide had minor effects on lipid parameters. Some inconsistent favorable effects were observed in AWARD-3 (decrease in LDL cholesterol), AWARD-4 (increase in HDL cholesterol), and AWARD-1 (decrease

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in triglycerides) [34–36]. In a CV meta-analysis of Phase 2 and 3 studies (AWARD-6 not included), a total of 51 patients [dulaglutide: 26 ($N = 3,885$) (0.67%); all comparators: 25 ($N = 2,125$) (1.18%)] experienced at least one CV event (death due to CV causes, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina). The results indicate that there was no increase in CV risk with dulaglutide compared with control therapies [41,42].

Dulaglutide anti-drug antibodies (ADA)

In the AWARD-1 through six studies, treatment-emergent dulaglutide antidrug antibodies (ADA) were detected in 1–2.8% of dulaglutide-treated patients. Among patients with treatment-emergent dulaglutide ADAs, limited numbers of patients developed native sequence GLP-1 (nsGLP-1) cross-reactive antibodies or injection site reactions. Dulaglutide registration information indicate that across the four Phase 2 and five Phase 3 clinical studies (not including AWARD-6), overall 64 (1.6%) dulaglutide-treated patients developed ADAs to dulaglutide. Of the 64 patients that developed ADAs, 34 patients (0.9% of the overall population) had dulaglutide-neutralizing antibodies, and 36 patients (0.9% of the overall population) developed antibodies against native GLP-1 [28,43]. No patients with treatment-emergent dulaglutide ADAs reported systemic hypersensitivity reactions including those who developed antibodies against native GLP-1. In AWARD-6, three patients developed ADAs (1%), two patients developed dulaglutide-neutralizing antibodies (1%), and no patients developed antibodies against native GLP-1 [39]. Because of low incidence of dulaglutide ADAs, and variability of glycemic response, no assessment of potential interaction was considered appropriate.

Discussion

Currently, GLP-1 RAs are identified among alternative first line treatment as well as combination therapy options for the treatment of T2DM [44,45]. Dulaglutide is a once-weekly GLP-1 RA, which is administered subcutaneously via the single-dose pen [46]. Dulaglutide has shown superior or non-inferior glycaemic control in all Phase 3 studies compared with multiple active comparators, including metformin, sitagliptin, exenatide BID, liraglutide, and insulin glargine, in a wide T2DM population at different stages of diabetes. The efficacy of dulaglutide was demonstrated by consistent, clinically relevant HbA1c reductions when used as a monotherapy or combination therapy. Glycaemic responses to dulaglutide were persistent and were maintained to final study endpoints up to 104 weeks. Dulaglutide-treated patients achieved an early, near-maximal improvement in FBG (within 2 weeks) [34,35,40], indicating FBG can be used as an early clinical measure of glycaemic response to dulaglutide.

Across all AWARD studies, the proportions of patients achieving HbA1c targets of <7.0% (53.0 mmol/mol) were significantly greater when treated with dulaglutide 1.5 mg (between 53%–78%) compared with metformin, sitagliptin, exenatide, and glargine, while similar proportions achieved the same target with liraglutide (68%). The decrease in HbA1c in response to dulaglutide 1.5 mg ranged from −0.78% to −1.64% (−8.5 to −17.9 mmol/mol) depending on baseline glycaemic status (Figure 2, Supplementary Table 3). In the head-to-head studies (AWARD-1 and AWARD-6), dulaglutide was superior to exenatide BID and non-inferior to liraglutide [35,39]. It is also important to note that dulaglutide 1.5 mg achieved superior glycaemic control (Figures 2 and 3) with lower rates of hypoglycaemia (Table 4) and weight loss or less weight gain (Figure 4, Supplementary Table 3) compared with glargine on a background treatment with glimepiride and metformin or lispro with or without metformin. These results support once weekly dulaglutide can be used as an effective alternative treatment to basal insulin in T2DM patients. In addition, dulaglutide significantly increased beta cell function (measured as HOMA2%B). Increases in HOMA2%B were significantly higher with dulaglutide compared with metformin [34], sitagliptin [37,40], and exenatide BID [35], and similar increased were observed with dulaglutide and liraglutide [39].

The GLP-1 RA class has been shown in numerous clinical studies to promote weight loss [47–50]. In all six Phase 3 studies, dulaglutide 1.5 mg resulted in weight reduction. In three of the five Phase 3 studies, dulaglutide 0.75 mg was associated with weight reduction. Dulaglutide 1.5 mg used as monotherapy, or as an add-on to stable doses of metformin, resulted in weight loss of 2.3–3.0 kg over a period of 6–12 months [51–53]. In head-to-head comparisons, dulaglutide 1.5, and exenatide BID therapy resulted in similar weight reductions while patients on dulaglutide 0.75 mg had less weight loss compared with exenatide BID. In AWARD-6, while both groups had significant weight reduction, liraglutide resulted in a slightly greater body weight loss (3.6 kg) compared with dulaglutide 1.5 mg (2.9 kg). Body weight loss observed with dulaglutide 1.5 mg was generally sustained for 1 to 2 years (Table 2).

The most commonly reported adverse events are GI-related, including nausea, diarrhea, and vomiting. The onset of nausea and vomiting occurs early after drug

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initiation and attenuates quickly. These GI-related AEs, for dulaglutide 1.5 mg, are similar to dose titrated exenatide BID or liraglutide 1.8 mg in head-to-head comparisons (Table 3). Consistent with the mechanism of action for dulaglutide (potentiation of glucose-dependent insulin secretion), when dulaglutide was used as monotherapy or added to a non-insulin-secretagogue OAM background therapy, the rates of total and severe hypoglycaemia were generally low, and similar to active comparators. Treatment with insulin-secretagogue therapies or insulin is known to increase the risk of hypoglycaemia. Importantly, when combined with glimepiride in AWARD-2, the total hypoglycaemia rate was lower in patients treated with dulaglutide 1.5 mg compared with insulin glargine, despite better glycaemic control. In AWARD-4, the percentage of patients achieving an HbA1c $<7.0\%$ (53.0 mmol/mol) without documented symptomatic, or without nocturnal or severe hypoglycaemia, was significantly higher for dulaglutide 1.5 mg compared with glargine [36].

The AWARD program implemented a consistent process to identify and independently adjudicate potential pancreatitis, with seven total adjudicated events (four in dulaglutide, three active comparators) observed [41]. Dulaglutide demonstrated an effect on pancreatic enzymes, as has been previously reported with the GLP-1 RA class [54–56]. In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone noted in routine serial assessments were not predictive of acute pancreatitis. There has been one report of MTC in a patient who received dulaglutide 2.0 mg; this cancer was assessed and determined to be preexisting. Consistent with other GLP-1 RAs, treatment with dulaglutide is associated with changes to parameters implicated in cardiovascular risk, including reduction in body weight, small but significant decreases in SBP for dulaglutide 1.5 mg, and small increases in HR [57]. Cardiovascular adverse events were comparable between dulaglutide and other comparators [42]. Dulaglutide immunogenicity was low with only 1–2.8% of patients developed treatment-emergent dulaglutide ADAs [43].

In summary, efficacy data from long-term, multinational Phase 3 studies demonstrate that dulaglutide is consistently efficacious in reducing HbA1c relative to active comparators (metformin, sitagliptin, exenatide, and insulin glargine) and comparable with liraglutide. However, it is important to note some of the unique study design limitations observed in some of the AWARD studies. Treatment with dulaglutide 1.5 mg resulted in a consistent decrease in HbA1c ranging from -1.08% to -1.64% in five out of the six studies, with the exception of the monotherapy study. It is important to emphasize that in the monotherapy study the mean endpoint HbA1c and the percentage of patients achieving HbA1c targets in response to with dulaglutide were within the expected range. However, the low baseline HbA1c and the short washout period in the monotherapy study led to a smaller than expected decrease in HbA1c (-0.78%). In the two insulin glargine studies, although strict enforcement of the insulin titration algorithms could not be achieved, the rates of hypoglycaemia events were still higher in the glargine arms, which may have limited the physician's ability to continue to increase insulin doses. When dulaglutide was compared with glargine in patients who were using background lispro, lispro doses were higher in the dulaglutide arms, and therefore the effect of the different lispro doses between groups could not be fully accounted for. On the other hand, the dulaglutide 1.5 arm, while having higher lispro doses, had lower hypoglycaemia rates compared with glargine, indicating that dulaglutide may be considered as an alternative treatment for patients with increased risk of hypoglycaemia. The open-label design in the two insulin glargine studies and exenatide and liraglutide studies is an additional limitation, which could have affected physicians' and patients' behavior.

Other general limitations to these studies include lack of data pertaining to the use of dulaglutide with basal insulin or SGLT-2 inhibitors. Also limitations include the exclusion of certain patient populations with recent history of clinically significant CV disease, severely decreased kidney function, and history of pancreatitis or MTC. Therefore, data regarding the effects of dulaglutide in these patient populations are currently limited. Although dulaglutide does not increase serum calcitonin levels, dulaglutide is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2, and should not be used in patients with history of pancreatitis [28]. It is also advised to monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions due to the increased risk of developing volume depletion that was observed with other GLP-1 RAs [58–60]. Long-term cardiovascular safety in patients at high risk for CV events is currently being assessed in the ongoing REWIND cardiovascular outcomes study (Trial NCT01394952). The ongoing AWARD-7 study is evaluating the effects of dulaglutide in patients with moderate and severe chronic kidney disease (Trial NCT01621178).

In conclusion, overall, dulaglutide is generally well tolerated with a safety profile consistent with other GLP-1 RAs. When considering dulaglutide's glycemic efficacy together with low risk of hypoglycaemia, and weight loss potential, dulaglutide is emerging as a promising new GLP-1 RA for the treatment of T2DM.

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Conflicts of interest

J.J. has served on advisory panels for Roche Diagnostics, Janssen Pharmaceuticals, Novo Nordisk, Eli Lilly and Company, Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb Company, and Medtronic; has received research support from Novo Nordisk; and has been on a speaker's bureau for AstraZeneca, Pfizer, Eli Lilly and Company, Novo Nordisk, and Boehringer Ingelheim. G.G. received research support from AstraZeneca, Eli Lilly and Company, Merck & Co., Novo Nordisk and Sanofi; and has served on the speakers' bureau of AstraZeneca,

Boehringer Ingelheim, Eli Lilly and Company, GlaxoSmithKlein, Janssen Pharmaceuticals, Merck & Co., Novo Nordisk, and Sanofi. T.B. has served on speakers bureaus for Eli Lilly and Company, Sanofi, Novo Nordisk, Boehringer Ingelheim, Amgen, Astra Zeneca, and Merck; and received research support from Eli Lilly and Company, Sanofi, Novo Nordisk, Astra Zeneca, Merck, Lexicon, Nuskin, and Boehringer Ingelheim. F.G. has served on an advisory panel for AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb Company, Eli Lilly and Company, Janssen Pharmaceuticals, Roche Pharmaceuticals, Takeda Pharmaceutical Company, Ltd., Merck Sharp & Dohme Limited, Novo Nordisk, Inc, and Sanofi. F.G. has received research support for Astra Zeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Eli Lilly and Company, Lifescan Animas Inc., and Sanofi. FTB and RTH are employees and shareholders of Eli Lilly and Company.

Supporting information

Supporting information may be found in the online version of this article.

Supplementary Table 1. Summary of Phase 2 Dose Titration and Dose Response Studies
Supplementary Table 2. Demographics and Baseline Characteristics
Supplementary Table 3. Summary of Clinical Efficacy at Primary Endpoint

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