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ORIGINAL ARTICLE

Placebo-controlled, randomized trial of the addition of once-weekly glucagon-like peptide-1 receptor agonist dulaglutide to titrated daily insulin glargine in patients with type 2 diabetes (AWARD-9)

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Aim: To compare the addition of weekly dulaglutide vs the addition of placebo to titrated glargine in patients with type 2 diabetes (T2D) with sub-optimum glycated haemoglobin (HbA1c) concentration.

Materials and Methods: Patients (N = 300) from this phase III, double-blind, parallel-arm, placebo-controlled study were randomized to weekly subcutaneous injections of dulaglutide 1.5 mg or placebo with titrated daily glargine (mean ± standard deviation baseline dose: 39 ± 22 U), with or without metformin (≥1500 mg/d). The primary endpoint was superiority of dulaglutide/glargine to placebo/glargine with regard to change from baseline in HbA1c level at 28 weeks.

Results: Least squares (LS) mean ± standard error (s.e.) HbA1c changes from baseline were −1.44 ± 0.09% (−15.74 ± 0.98 mmol/mol) with dulaglutide/glargine and −0.67 ± 0.09% (−7.32 ± 0.98 mmol/mol) with placebo/glargine at 28 weeks (LS mean difference [95% confidence interval] −0.77% [−0.97, −0.56]; $P < .001$). Body weight decreased with dulaglutide/glargine and increased with placebo/glargine (LS mean difference: −2.41 ± 0.39 kg; $P < .001$). Increases from baseline in mean glargine dose were significantly smaller with dulaglutide/glargine vs placebo/glargine (13 ± 2 U [0.1 ± 0.02 U/kg] vs 26 ± 2 U [0.3 ± 0.02 U/kg], respectively; $P < .001$; LS mean ± s.e. final dose: dulaglutide/glargine, 51 ± 2 U; placebo/glargine, 65 ± 2 U). The hypoglycaemia rate (≤3.9 mmol/L threshold) was 7.69 ± 15.15 and 8.56 ± 16.13 events/patient/year, respectively ($P = .488$). One episode of severe hypoglycaemia occurred in the dulaglutide/glargine group. Common gastrointestinal adverse events with dulaglutide were nausea (12.0%), diarrhoea (11.3%) and vomiting (6.0%).

Conclusions: Weekly dulaglutide 1.5 mg added to basal insulin is an efficacious and well tolerated treatment option for patients with T2D.

KEYWORDS

AWARD-9, dulaglutide, GLP-1 receptor agonists, insulin glargine, type 2 diabetes

1 | INTRODUCTION

In type 2 diabetes (T2D), the addition of insulin or glucagon-like peptide-1 receptor agonists (GLP-1RAs) is needed when oral antihyperglycaemia medications do not maintain adequate glycaemic control. Titrated basal insulin glargine added to oral antihyperglycaemia medication therapy is a common approach to the initiation of injectable therapy[1,2]; however, many patients are unable to achieve

glycaemic targets and, in those who do, hypoglycaemia risk increases,[3] and weight gain is common.[3,4] Treatment with basal insulin often provides initial glycaemic improvements, but subsequent deterioration occurs in most patients, requiring further insulin dose uptitration.[5,6]

Interest in the addition of GLP-1RAs to basal insulin therapy has recently increased as a result of their complementary effects on glycaemic control and their ability to increase satiety and induce weight loss.[7] GLP-1RAs may also lead to a reduction in insulin dose by enhancing endogenous insulin secretion, which may contribute to the beneficial effects on body weight and hypoglycaemia risk.[8] Combination therapy can be administered using separate preparations of each component (flexible-dosing strategy) or using combination preparations containing both agents (fixed-ratio strategy).[9–11] Twice-daily exenatide combined with titrated glargine improved glycaemic control with modest weight loss and without increasing hypoglycaemia risk vs placebo.[10,11] Similar results were observed with once-daily lixisenatide or once-weekly albiglutide[12,13] and with fixed combinations of insulin degludec and liraglutide or glargine and lixisenatide.[14,15]

The flexible combination regimen with basal insulin and once-weekly GLP-1RAs is of interest because it reduces the number of injections compared with combinations with once- or twice-daily GLP-1RAs, thus decreasing treatment burden. The AWARD-9 (**A**ssessment of **W**eekly **A**dminist**R**ation of LY2189265 [dulaglutide] in **D**iabetes-9) study compared the addition of dulaglutide vs the addition of placebo to glargine, titrated to target. While there have been previous trials conducted with the combination of weekly GLP-1RA and basal insulin therapy,[13] this was the first study to employ intensive insulin dose titration in both arms using the treat-to-target (TTT) algorithm. The study regimens were assessed with respect to their effects on glycaemic control, body weight and relevant safety outcomes during a 28-week treatment period. Because of scarcity of data on patient-reported outcomes measures (PROMs) with the combination regimen, we assessed several PROMs.

2 | MATERIALS AND METHODS

2.1 | Study design and participation

This phase III, multicentre, double-blind, parallel-arm, placebo-controlled study compared the safety and efficacy of dulaglutide 1.5 mg with placebo, when both were added to daily insulin glargine titrated to target. Patients were randomized 1:1 to receive weekly subcutaneous injections of dulaglutide 1.5 mg or placebo with glargine according to a computer-generated random sequence using an interactive voice response system. Adults with T2D (glycated haemoglobin [HbA1c] ≥7.0% [≥53 mmol/mol] and ≤10.5% [≤91.3 mmol/mol]) were eligible for the study if they had a body mass index ≤45 kg/m^2 and were on a stable dose of glargine (with or without metformin, ≥1500 mg/d) for ≥3 months prior to visit 1. The study had two periods: a screening/lead-in period (3 weeks from screening to randomization) and a treatment period (28 weeks from randomization to the study end, including a 4-week stabilization phase, followed by a 24-week titration phase). During the lead-in period, patients were required to provide self-monitored plasma glucose (SMPG) measurements; only patients who required an increase in glargine dose at randomization as a result of fasting plasma glucose (FPG) above the target as per the TTT algorithm were eligible (Table S1).[1]

The study was conducted in accordance with the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, as well as the International Conference on Harmonisation Good Clinical Practices Guideline. The protocol was approved by local institutional review boards. All patients provided written informed consent prior to any procedure. The study was registered with ClinicalTrials.gov (NCT02152371).

2.2 | Procedures

During the lead-in period, insulin dose assessments occurred once weekly and insulin doses were adjusted according to the algorithm only when needed to prevent the occurrence of hypoglycaemia or severe hyperglycaemia. After randomization, during the initial 4-week stabilization phase, insulin dose was assessed twice weekly. The glargine dose remained unchanged if the baseline HbA1c concentration was >8.0% or was decreased by 20% if HbA1c was ≤8.0% immediately after randomization to avoid hypoglycaemia in patients receiving dulaglutide. Additional insulin dose adjustments during this phase were required only in case of the occurrence of hypoglycaemia or severe hyperglycaemia. After the stabilization phase, the insulin dose was adjusted without limitations in both arms until the trial end. Office visits during the treatment period were weekly or bi-weekly during the first 2 months and thereafter every 4 to 6 weeks.

Compliance with treatment regimen was assessed by: (1) administration of study drug at every visit; patients were considered compliant if taking at least 75% of the required doses; and (2) compliance with the TTT algorithm after 6, 8 and 12 weeks of therapy, measured by the proportion of assessments performed correctly, the proportion of assessments that required a dose change, and the proportion of assessments for which the required dose changes were correctly followed.

Patients requiring an additional intervention as a result of severe, persistent hyperglycaemia were to stop the study drug and discontinue the study after the early termination visit. Patients who discontinued the study drug for any other reason were also required to discontinue the study at the same time.

2.3 | Outcomes

The primary objective was to demonstrate superiority of addition of dulaglutide over the addition of placebo to insulin glargine titrated to target with regard to change in HbA1c from baseline to week 28. Key secondary objectives included treatment comparisons for change from baseline in body weight, percentage of patients achieving HbA1c <7.0% (<53 mmol/mol) and fasting serum glucose (FSG) from the central laboratory at 28 weeks. Other secondary objectives included treatment comparisons for percentage of patients achieving HbA1c targets of ≤6.5% (≤48 mmol/mol), change in 7-point SMPG profiles, and mean daily glargine doses. The following composite outcomes were analysed: percentage of patients achieving HbA1c

targets of <7.0% (<53 mmol/mol) without weight gain (<0.1 kg) at 28 weeks; percentage of patients achieving HbA1c targets of <7.0% (<53 mmol/mol) without documented symptomatic hypoglycaemia during the maintenance period (weeks 12-28; the period when glargine dose is expected to be stable); and percentage of patients achieving HbA1c targets of <7.0% (<53 mmol/mol) without weight gain (<0.1 kg) and without documented symptomatic hypoglycaemia during the maintenance period.

Safety outcomes included adverse events (AEs), laboratory variables, vital signs, ECGs and dulaglutide anti-drug antibodies. AEs of special interest were pancreatitis confirmed by adjudication, thyroid neoplasms, cardiovascular events confirmed by adjudication and hypersensitivity reactions (see Appendix S1 for details on adjudication). All laboratory measures were performed using the central laboratory (Quintiles Laboratories LTD, Marietta, Georgia and Quintiles Laboratory Europe, West Lothian, UK).

The hypoglycaemia rate and incidence of documented symptomatic, asymptomatic, probable symptomatic, severe, nocturnal and total hypoglycaemia were also assessed (see Appendix S1). Total hypoglycaemia included severe, documented symptomatic, asymptomatic or probable symptomatic events, defined as plasma glucose ≤3.9 mmol/L,[16] and unspecified hypoglycaemia. Severe hypoglycaemia was defined as an event that required the assistance of another person to actively administer therapy.

Patients' quality of life was assessed with regard to PROMs at baseline and weeks 12 and 28 using various questionnaires. The EQ-5D-5 L assessed the patient's health status related to mobility, self-care, usual activities, pain/discomfort, and anxiety/depression[17]; the 18-item Diabetes Health Profile (DHP-18) questionnaire assessed psychological distress, barriers to activity, and disinhibited eating, and included disease-specific health-related quality of life questions adapted for use in patients with T2D[18]; the Impact of Weight on Self-Perception (IW-SP) questionnaire was used to assess how often body weight affected patient happiness with his/her appearance and how often the patient felt self-conscious in public.[19] The modified Medication Delivery Device Assessment Battery (MDDAB), assessed at baseline and weeks 6 and 28, evaluated patient perceptions regarding the use of the dulaglutide and placebo injection devices (identical in both arms).[20]

2.4 | Statistical analyses

Approximately 308 randomized patients (n = 154/group) and 246 completers (n = 123/group) were expected to provide 90% power to show superiority of dulaglutide 1.5 mg vs placebo for change from baseline in HbA1c at 28 weeks at the 2-sided significance level of 0.05, assuming that dulaglutide reduced HbA1c by 0.5% more than placebo, with a standard deviation (s.d.) of 1.2%. Efficacy and safety analyses were performed using the intention-to-treat (ITT) population, defined as all randomized patients who took ≥1 dose of study medication. A mixed-model for repeated measures (MMRM) was used as the primary analysis model, with treatment, pooled country, metformin use, visit and treatment-by-visit as fixed effects, baseline as a covariate, and patient as a random effect. An MMRM was also used for analyses of other continuous measures. The chi-squared test was used for categorical measures. The percentages of patients achieving HbA1c targets were analysed using a logistic regression model for repeated measures with factors of treatment, pooled country, baseline HbA1c, metformin use, visit and visit-by-treatment interaction. Hypoglycaemia rate was analysed using a generalized linear model with negative binomial distribution. To control type I error, a graphical testing scheme was used to compare treatments regarding selected secondary endpoints (HbA1c target of <7.0%, body weight and FSG).[21]

Exploratory PROM analyses of covariance included fixed effects for treatment, baseline HbA1c strata, pooled country, metformin use and baseline score as a covariate. Last observation carried forward (LOCF) was used to impute missing post-baseline values, and treatment contrasts were computed. All analyses were implemented using SAS version 9.1 or higher.

3 | RESULTS

Overall, 300 patients were randomized to dulaglutide 1.5 mg or placebo arms (n = 150/group). Twelve (8%) patients in the dulaglutide/glargine and 16 (10.7%) in the placebo/glargine group discontinued the study early, most commonly through patient decision (dulaglutide, n = 3 [2.0%]; placebo, n = 7 [4.7%]) and because of AEs (dulaglutide, n = 6 [4.0%]; placebo, n = 2 [1.3%]; Figure 1). Baseline characteristics were similar in the treatment groups (Table 1).

3.1 | Efficacy

Least squares (LS) mean ± s.e. changes from baseline in HbA1c were −1.44 ± 0.09% (−15.74 ± 0.98 mmol/mol; $P < .001$) with dulaglutide/glargine and −0.67 ± 0.09% (−7.32 ± 0.98 mmol/mol; $P < .001$) with placebo/glargine, resulting in final HbA1c of 6.92 ± 0.09% and 7.69 ± 0.09%, respectively, at 28 weeks. Reductions with dulaglutide/glargine were significantly greater than placebo/glargine, with a between-group difference of −0.77% (95% confidence interval [CI] −0.97 to −0.56, $P < .001$; Figure 2A and Figure S1A), equivalent to −8.42 mmol/mol.

A significantly greater percentage of patients in the dulaglutide/glargine group (66.7%) vs the placebo/glargine group (33.3%) achieved HbA1c <7.0% (<53 mmol/mol) and a significantly greater percentage of dulaglutide/glargine patients (50.0%) achieved HbA1c ≤6.5% (≤48 mmol/mol) vs placebo/glargine (16.7%) at 28 weeks ($P < .001$, both comparisons; Figure 2B).

Significant decreases from baseline in FSG and plasma glucose from the 7-point SMPG profiles were observed with both dulaglutide 1.5 mg and placebo at 28 weeks ($P < .001$, both treatment arms for each variable). Dulaglutide/glargine treatment reduced FSG ($P < .001$; Figure 2C) and plasma glucose from the 7-point SMPG profiles at 28 weeks significantly more than placebo/glargine ($P \leq .007$; Figure 2D and Table S2). At 28 weeks, the proportions of patients reaching FPG <5.6 mmol/L did not significantly differ between the groups (dulaglutide/glargine, n = 66 [49.3%]; placebo/glargine, n = 50 [37.9%]; $P = .061$); a significantly greater proportion of dulaglutide/

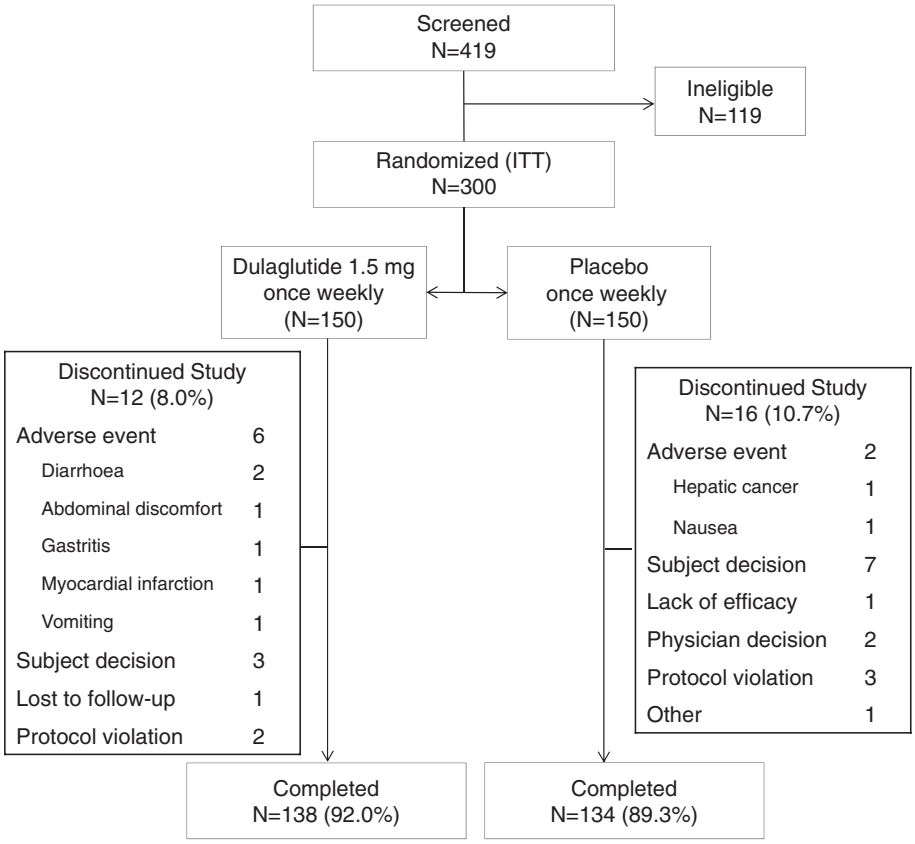

FIGURE 1 Patient disposition

glargine patients reached FPG <6.7 mmol/L vs placebo/glargine patients (dulaglutide/glargine, n = 115 [85.8%]; placebo/glargine, n = 93 [70.5%]; P = .002).

Dulaglutide/glargine treatment significantly reduced body weight from baseline vs placebo/glargine (LS mean ± s.e. −1.91 ± 0.30 kg, P < .001 and 0.50 ± 0.30 kg, P = .093, respectively) with a treatment difference of −2.41 ± 0.39 kg (95% CI −3.19, −1.64; P < .001; Figure 2E and Figure S1B). Figure S2 provides a scatter plot for body weight changes vs change in insulin dose.

A summary of results of assessments of composite outcomes is presented in Table S3. A significantly greater percentage of patients achieved HbA1c <7.0% (<53 mmol/mol) without weight gain at 28 weeks and/or documented symptomatic hypoglycaemia during the maintenance period in the dulaglutide/glargine group than in the placebo/glargine group (P < .001, all comparisons).

The LS mean ± s.e. increases from baseline in daily glargine dose were significantly smaller with dulaglutide/glargine (13 ± 2 U [0.1 ± 0.02 U/kg]) vs placebo/glargine (26 ± 2 U [0.3 ± 0.02 U/kg]); P < .001 at 28 weeks (final LS mean ± s.e. dose: dulaglutide/glargine 51 ± 2 U; placebo/glargine 65 ± 2 U; Figure S1C). Figure S3 and Table S4 provide additional data by subgroups, based on the need to adjust insulin dose at randomization when HbA1c was <8%. A total of 287 patients (dulaglutide/glargine, 145 [96.7%]; placebo/glargine, 142 [94.7%]) had ≥1 insulin dose assessment (Table S5). Approximately 90% of the assessments in both groups were performed correctly. Approximately 43% and 17% of patients in both groups did not follow assessment outcomes 1 or more times as a result of patient or investigator decision, respectively. The most frequent reason for physician and patient decision not to follow the algorithm was hypoglycaemia (approximately 25% and 11% of patients overall, respectively; no significant differences between the groups).

Significant improvements in PROMs were observed with dulaglutide/glargine for the IW-SP Transformed Total Score (LS mean difference 6.06; P = .019) and the DHP-18 Disinhibited Eating Domain Transformed Score (LS mean difference −4.50; P = .017) vs placebo/glargine at 28 weeks. There were no differences for other PROMs. The majority of patients (95%) reported that the dulaglutide injection device was "easy" or "very easy." The device features that were rated highest by the patients were those related to features of the needle (ie, not having to touch the needle, not having to attach the needle, and automatic insertion). Approximately 90% of patients were satisfied with their overall injection experience with the dulaglutide and placebo injection devices at 28 weeks.

3.2 | Safety

Nine patients (6.0%) in the dulaglutide/glargine group and 7 (4.7%) in the placebo/glargine group experienced serious AEs (Table S6). No deaths occurred during the study. A significantly greater percentage of dulaglutide/glargine patients reported treatment-emergent adverse events (TEAEs) vs placebo/glargine (64% vs 50%; P = .014), primarily because of a higher incidence of gastrointestinal AEs with dulaglutide, especially nausea, diarrhoea and vomiting (12.0%, 11.3%, and 6.0%, respectively; Table 2). Overall, 8 patients (2.7%) discontinued the study because of AEs (dulaglutide/glargine, n = 6 [4.0%]; placebo/glargine, n = 2 [1.3%]; Table 2), of whom 6 discontinued because of gastrointestinal-related AEs (dulaglutide/glargine, n = 5 [3.3%]; placebo/glargine, n = 1 [0.7%]).

TABLE 1 Baseline characteristics

Variable	Dulaglutide 1.5 mg once weekly (N = 150)	Placebo once weekly (N = 150)
Sex, n (%)		
Men	85 (56.7)	88 (58.7)
Women	65 (43.3)	62 (41.3)
Age, years	60.2 (9.5)	60.6 (10.1)
Age ≥65 years, n (%)	55 (36.7)	58 (38.7)
Race, n (%)		
Asian	0 (0.0)	1 (0.7)
Black or African-American	5 (3.3)	6 (4.0)
Multiple	1 (0.7)	3 (2.0)
White	143 (95.3)	138 (92.0)
Ethnicity, n (%)		
Hispanic or Latino	26 (17.3)	25 (16.7)
Not Hispanic or Latino	104 (69.3)	104 (69.3)
Not reported	20 (13.3)	21 (14.0)
Weight, kg	93.3 (17.5)	92.6 (17.1)
Body mass index, kg/m^2	32.8 (4.9)	32.6 (4.9)
Diabetes duration, years	13.0 (7.5)	13.3 (7.7)
HbA1c, %	8.4 (0.9)	8.3 (0.8)
HbA1c, mmol/mol	68 (9.8)	67 (8.8)
FSG, mmol/L	8.7 (2.6)	8.7 (2.6)
SBP, mm Hg	135.0 (14.0)	137.7 (16.6)
DBP, mm Hg	78.3 (9.0)	78.5 (8.7)
Insulin glargine dose, U	40.7 (23.1)	36.6 (21.5)
Duration of glargine use, years	2.18 (0.2)	2.3 (0.3)
Patients on metformin, n (%)	134 (89.3)	131 (87.3)

Data are presented as mean (s.d.) unless otherwise indicated.

Abbreviations: DBP, (sitting) diastolic blood pressure; SBP, (sitting) systolic blood pressure.

The incidence of total hypoglycaemia was similar between groups (dulaglutide/glargine, n = 82 [54.7%]; placebo/glargine, n = 76 [50.7%]). The mean ± s.d. event rate/patient/year was 7.69 ± 15.15 with dulaglutide/glargine vs 8.56 ± 16.13 with placebo/glargine (P = .488; Figure S1D and Table S7). One (0.7%) dulaglutide/glargine-treated patient experienced an episode of severe hypoglycaemia. The patient recovered and completed the trial.

No cases of acute pancreatitis were reported by investigators. Three events submitted for adjudication because of elevated pancreatic enzymes without symptoms of acute pancreatitis (all dulaglutide/glargine) did not meet the criteria for pancreatitis. Dulaglutide/glargine treatment significantly increased lipase (LOCF median change [Q1, Q3] 5 [−5, 14] U/L; P = .012) and pancreatic-amylase (p-amylase) levels (4 [0, 8] U/L, P < .001) vs placebo/glargine (0 [−5, 6] U/L and 1 [−2, 4] U/L, respectively) at 28 weeks. Mean ± s.e. percent changes from baseline in lipase and p-amylase were 24% ± 3% vs 8% ± 2% and 23% ± 3% vs 9% ± 2% for dulaglutide/glargine vs placebo/glargine, respectively (Table 2). Changes in total amylase were smaller but consistent with changes in p-amylase levels. There were no reports of C-cell-related AEs. Changes from baseline in median calcitonin values did not significantly differ.

No dulaglutide/glargine-treated patients developed treatment-emergent anti-drug antibodies (Table 2). Three patients reported TEAEs possibly related to a hypersensitivity reaction (dulaglutide/glargine, n = 2 [pruritus and allergic pruritus]; placebo/glargine, n = 1 [pruritus and erythaema]) that were all mild to moderate in intensity. Only the allergic pruritus was considered related to study drug by the investigator. A single TEAE related to injection site reaction was reported in the dulaglutide/glargine group (injection site haematoma).

4 | DISCUSSION

Combining agents from different glucose-lowering medication classes to improve glycaemic control and/or minimize side effects is the recommended approach to treat T2D.[22] In the present trial, we assessed the effects of once-weekly GLP-1RA dulaglutide vs placebo, when both are added to insulin glargine titrated to target, in insulin-treated patients with suboptimal HbA1c concentration. Clinically relevant glucose-lowering effects were observed in both groups, but the improvement with dulaglutide was significantly greater, with a similar risk of hypoglycaemia in the two groups. Dulaglutide/glargine reduced body weight vs modest increases observed with placebo/glargine.

Observational studies have shown that a large proportion of patients in clinical settings are not achieving their glycaemic goals after initiation of basal insulin therapy.[23,24] One possible reason may be insufficient insulin dose titration, as indicated by patients' fasting hyperglycaemia in the absence of hypoglycaemia.[13,25] In AWARD-9, we compared intensive, treat-to-target, insulin glargine dose uptitration, alone or in combination with weekly GLP-1RA dulaglutide, in placebo-controlled conditions. In the placebo/glargine group, a clinically relevant reduction from baseline in HbA1c of 0.67% (−7.32 mmol/mol) confirmed the appropriateness of the comparator. This is further supported by the consistency of reduction in HbA1c in the comparator group, with reductions observed with titrated glargine alone or in combination with add-on prandial insulin reported in the literature (ranging from −0.4% to −1.04% [−4.37 to −11.37 mmol/mol]),[10,13] and the endpoint FPG (6.3 mmol/L) being lower than in these other similar studies (range 6.8-8.0 mmol/L). Dulaglutide/glargine decreased HbA1c significantly more than placebo/glargine, which can be explained by greater improvements in both fasting/pre-meal and postprandial control, supporting the rationale for combining basal insulin with a long-acting GLP-1RA.

Differences in HbA1c reduction between treatments must be assessed in relation to insulin dose titration, achievement of FPG targets and risk of hypoglycaemia; that is, key criteria for dose adjustment within the TTT algorithm. According to the protocol, a 20% decrease in insulin dose during the stabilization period for patients with HbA1c ≤8% was needed to avoid hypoglycaemia in the dulaglutide group, which favoured the dulaglutide/glargine combination during the initial 4 weeks because patients were not allowed to titrate insulin doses during this phase, except in case of hypoglycaemia or severe hyperglycaemia. To allow insulin doses to be adjusted in a timely manner to compensate for the stabilization period, an extended dose titration period of 24 weeks was part of the trial

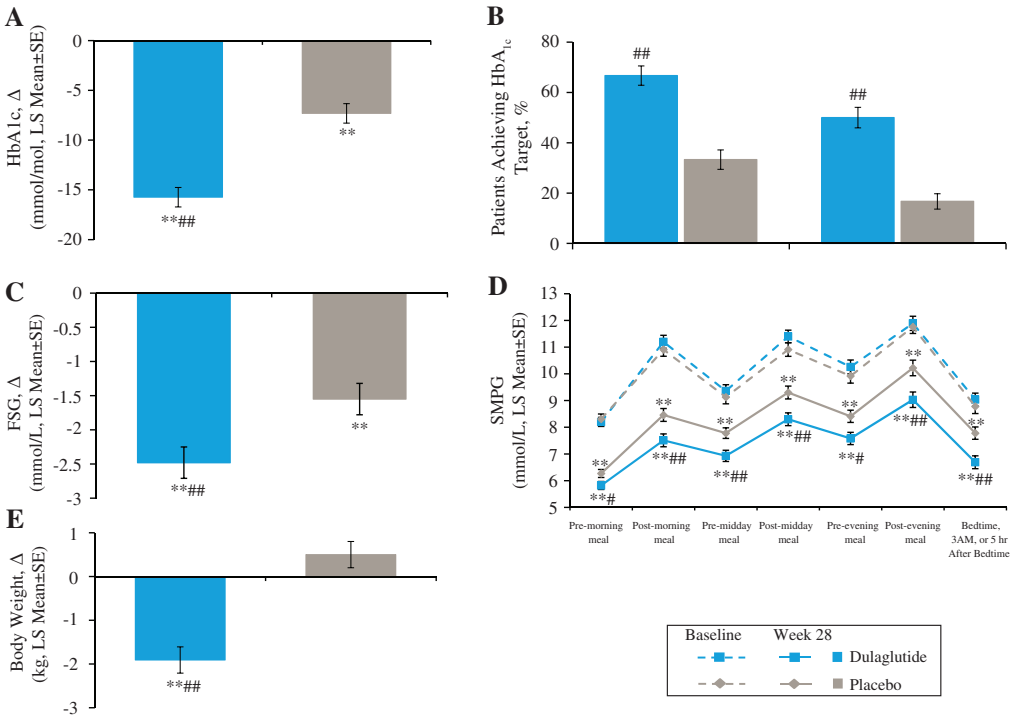

FIGURE 2 Efficacy of once-weekly dulaglutide 1.5 mg vs placebo, both added to titrated insulin glargine. A, Change in HbA1c from baseline to week 28 (mmol/mol), MRMM. B, Percentage of patients achieving HbA1c targets, MRMM. C, Change in FSG concentrations from baseline to week 28, as measured by a central laboratory (mmol/L), MRMM. D, 7-point SMPG (mmol/L), MMRM. E, Body weight from baseline to 28 weeks (kg), MRMM. $^{*}P < .05$, $^{**}P < .001$ change from baseline; $^{\#}P < .05$, $^{\#\#}P < .001$ dulaglutide vs placebo

design. Patients in the placebo/glargine group increased insulin doses more than those in the dulaglutide/glargine group during this phase, with significant differences achieved between weeks 12 and 18. We observed only modest and similar changes in both groups thereafter until the trial endpoint at week 28. Consistent with data for insulin doses, most of the effect on FPG was obtained after 12 weeks of therapy (Table S2), suggesting that the duration of the treatment period was appropriate for planned assessments in AWARD-9. We also assessed insulin dosing and FSG control for patients with and without 20% insulin dose adjustment after randomization (Table S4 and Figure S3). These data showed that patients who required a 20% insulin dose decrease at randomization (approximately one-third of the patients in each treatment group) were able to adjust their insulin dose in a timely manner and achieve most of the FSG reduction after 12 and 18 weeks of treatment. The results were similar in the patient subgroups that did not require initial insulin dose reduction. During the final 16 weeks of treatment, insulin doses and FSG changed only modestly and with similar magnitude across the treatment groups and subgroups per baseline HbA1c; therefore, it can be concluded that insulin dose adjustments required during the stabilization period did not have an impact on the final outcome of this trial. Additionally, between-group differences for FPG-lowering were much smaller than the differences at other time points during the day, indicating the need for more intensive management of postprandial hyperglycaemia in many patients treated with a basal insulin-only regimen. Increasing the risk of hypoglycaemia with intensive uptitration of glargine is an additional factor that may explain limitations in achieving the HbA1c targets in the placebo/glargine group. Approximately 43% of patients in both groups reported not following the TTT algorithm one or more times. Fear of hypoglycaemia was the most frequent reason for avoiding insulin dose uptitration. The overall incidence of hypoglycaemia was similar in the two groups; therefore, the impact of hypoglycaemic episodes on insulin titration was also expected to be similar in the groups, despite much lower HbA1c with dulaglutide/glargine. Although a longer follow-up would be valuable to further assess the treatment effects on insulin dose and HbA1c, it is unlikely that the main conclusions based on the 28-week duration would differ with a longer observational period, taking into account observed changes in insulin dosing, fasting and postprandial glycaemia and the risk of hypoglycaemia in the two groups.

The addition of dulaglutide to glargine in the present study resulted in weight reduction vs modest weight gain with placebo/glargine, which is an important outcome in insulin-treated patients with T2D because they often gain weight after insulin dose uptitration. Similarly, a significantly greater number of patients in the dulaglutide/glargine group achieved the composite clinical outcomes of achieving HbA1c <7% without body weight gain and/or without documented symptomatic hypoglycaemia between weeks 12 and 28. As expected, the magnitude of body weight change correlated with the change in insulin dose in both groups, suggesting that body weight reduction in patients who received dulaglutide probably resulted from the known effect of this medication on appetite and because of the smaller insulin dose increase in that group compared with the placebo/glargine group (Figure S2). We applied several PROM instruments to assess patient-perceived benefits of study treatments. Patients in the dulaglutide/glargine group reported an improvement in how they perceived the impact of body weight on their

TABLE 2 Safety assessments during the 28 weeks

Variable	Dulaglutide 1.5 mg once weekly (N = 150)	Placebo once weekly (N = 150)
Deaths	0	0
Serious AEs[a]	9 (6.0)	7 (4.7)
TEAEs (patients with ≥1 TEAE)		
	96 (64.0)	75 (50.0)
TEAEs (≥5% patients in either group)		
Gastrointestinal disorders		
Nausea	18 (12.0)†	2 (1.3)
Diarrhoea	17 (11.3)*	6 (4.0)
Vomiting	9 (6.0)*	0 (0.0)
Dyspepsia	9 (6.0)*	0 (0.0)
Other		
Nasopharyngitis	6 (4.0)	14 (9.3)
Headache	6 (4.0)	6 (4.0)
Decreased appetite	10 (6.7)†	0 (0.0)
Study and/or study drug discontinuation because of AEs		
	6 (4.0)	2 (1.3)
Pancreatic enzymes, LOCF, median change (Q1,Q3), U/L		
Total amylase	5 (0, 13)†	1.5 (−3, 8)
P-amylase	4 (0, 8)†	1 (−2, 4)
Lipase	5 (-5, 14)*	0 (−5, 6)
Patients with values ≥2x ULN		
Total amylase	1 (0.7)	2 (1.3)
P-amylase	2 (1.3)	0 (0.0)
Lipase	13 (8.7)	4 (2.7)
Patients with values ≥3x ULN		
Total amylase	0 (0.0)	0 (0.0)
P-amylase	0 (0.0)	0 (0.0)
Lipase	2 (1.3)	0 (0.0)
Treatment-emergent dulaglutide anti-drug antibodies		
Dulaglutide anti-drug antibodies	0 (0.0)	2 (1.3)
Dulaglutide neutralizing anti-drug antibodies	0 (0.0)	0 (0.0)
nsGLP-1 neutralizing antibodies	0 (0.0)	0 (0.0)

Abbreviations: NA, not applicable; nsGLP-1, native sequence glucagon-like peptide-1; Q1 = 25th percentile; Q3 = 75th percentile; ULN, upper limit of normal.

Data are presented as n (%) unless specified.

[a]Reported serious adverse events are listed in Table S6.

*$P < .05$, †$P < .001$ dulaglutide vs placebo.

daily life, consistent with the difference in body weight changes between the groups. While the impact of diabetes therapies on body weight is often investigated in the clinical context of cardiovascular risk, these PROM data in patients receiving GLP-1RAs as an add-on intervention to insulin suggest that other patient-relevant improvements related to body weight may also be achieved.

Patients in the dulaglutide/glargine group experienced mild or moderate gastrointestinal AEs more often than those in the placebo/glargine group; 5 dulaglutide/glargine-treated patients discontinued the study because of gastrointestinal AEs. No cases of acute pancreatitis or thyroid tumours were reported. Dulaglutide increased the mean pancreatic enzyme levels within the normal range, a result that was similar to findings in other incretin studies, including those investigating dulaglutide. The clinical relevance of this change remains to be determined. No dulaglutide/glargine-treated patient developed dulaglutide anti-drug antibodies and the number of hypersensitivity or injection site reactions was low. These safety observations are similar to those already reported for dulaglutide.[26]

The present study has several limitations with respect to trial design. As discussed above, titration of glargine is an important potential confounding factor in trials that include a flexible insulin dosing strategy. Compliance with the TTT algorithm did not suggest any relevant differences between the groups with respect to using this dosing algorithm. Hypoglycaemia risk may have affected dose titration in both groups similarly, despite significant difference in HbA1c. Although the present study did not compare the dulaglutide/glargine regimen with other available treatment options for this study population (eg, addition of prandial insulin or a short-acting GLP-1RA), these data are important for an objective assessment of the combination therapy.

In conclusion, combination of once-weekly dulaglutide 1.5 mg with basal insulin glargine provides an effective and safe treatment option for patients with T2D already treated with basal insulin but who have hyperglycaemia and HbA1c concentration above their target range.

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Conflict of interest

P. P. has received research support from Eli Lilly and Company and serves on the speaker bureau for Sanofi-Aventis. P. N. has received research support from NovoNordisk, Eli Lilly and Company, Sanofi-Aventis, Takeda Pharmaceuticals International Inc., AstraZeneca, Roche, Pfizer, Purdue Pharma L.P. and Bristol-Myers Squibb. E. J. has received investigational grants from Astra Zeneca, Eli Lilly, GSK, Janssen, Merck Sharp & Dohme and NovoNordisk, consultancy fees from AstraZeneca, MSD and NovoNordisk, and is on the speaker bureau for Astra Zeneca, Eli Lilly and Company, Janssen, Merck Sharp & Dohme and NovoNordisk. M. J. D. has acted as consultant, advisory panel and board member for Novo Nordisk, Sanofi-Aventis, Eli Lilly and Company, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca and Janssen, is on the speaker bureau for Novo Nordisk, Sanofi-Aventis, Eli Lilly and Company, Merck Sharp & Dohme,

Boehringer Ingelheim, AstraZeneca, Janssen, Mitsubishi Tanabe Pharma Corporation and Takeda Pharmaceuticals International Inc., and has received research support from Novo Nordisk, Sanofi-Aventis and Eli Lilly and Company. T. I., H. J., B. W. and Z. M. are employees and/or shareholders for Eli Lilly & Company.

Author contributions

P. P., T. I., H. J. and Z. M. contributed to the trial design. P. P., P. N., E. J. and M. J.D. were trial investigators and participated in data collection. Z. M. was responsible for medical oversight during the trial. H. J. was responsible for the statistical considerations in the analysis and trial design. Z. M., B. W. and H. J. are the guarantors of this work and, as such, take responsibility for the integrity of the data and the accuracy of the data analysis. All authors participated in critical reviewing and interpreting the data for the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Pozzilli P, Norwood P, Jódar E, Davies MJ, Ivanyi T, Jiang H, Woodward B and Milicevic Z. Placebo-controlled, randomized trial on the addition of once-weekly glucagon-like peptide-1 receptor agonist dulaglutide to titrated daily insulin glargine in patients with type 2 diabetes (AWARD-9). *Diabetes Obes Metab*. 2017;19:1024–1031. https://doi.org/10.1111/dom.12937

Supplemental Appendix

Key exclusion criteria

Key exclusion criteria included patients with type 1 diabetes, use of any other glucose-lowering medications within the 3 months prior to Visit 1, serum calcitonin ≥20 pg/mL, serum creatinine ≥1·5 mg/dL (male) or ≥1.4 mg/dL (female) or a creatinine clearance <60 mL/min/1.73 m^2 (only in metformin-treated patients), history of pancreatitis, or recent CV event.

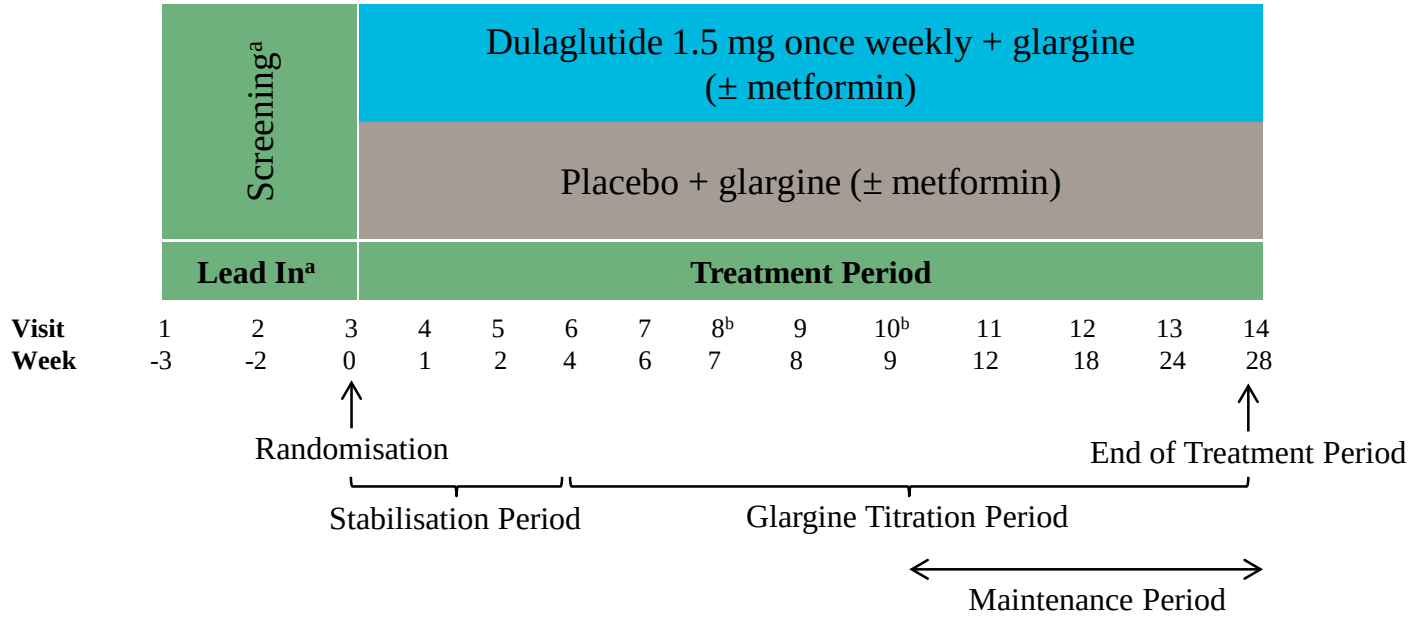
Details of adjudication

Deaths, nonfatal CV events, and pancreatitis events were adjudicated by an independent external committee (Duke Clinical Research Institute, Durham, NC, USA). Diagnostic criteria for acute pancreatitis included AEs of severe or serious abdominal pain, serum lipase or amylase values confirmed ≥3x the upper limit of normal (ULN), and/or characteristic findings of pancreatitis computed tomography (CT) scan or magnetic resonance imaging (MRI) confirmation.

Hypoglycaemia definitions

Documented symptomatic hypoglycaemia was defined as any time a patient felt that that they were experiencing symptoms and/or signs associated with hypoglycaemia, and had a plasma glucose ≤3.9 mmol/L or ≤3 mmol/L. Asymptomatic hypoglycaemia was defined as an event not accompanied by typical symptoms of hypoglycaemia, but with plasma glucose levels similar to documented symptomatic hypoglycaemia. Probable symptomatic hypoglycaemia was defined as an event during which symptoms of hypoglycaemia were not accompanied by a plasma glucose determination but that was presumably caused by plasma glucose ≤3.9 mmol/L] and unspecified hypoglycaemia was defined as events with missing data on symptoms of hypoglycaemia but with a measured plasma glucose levels similar to documented symptomatic hypoglycaemia.

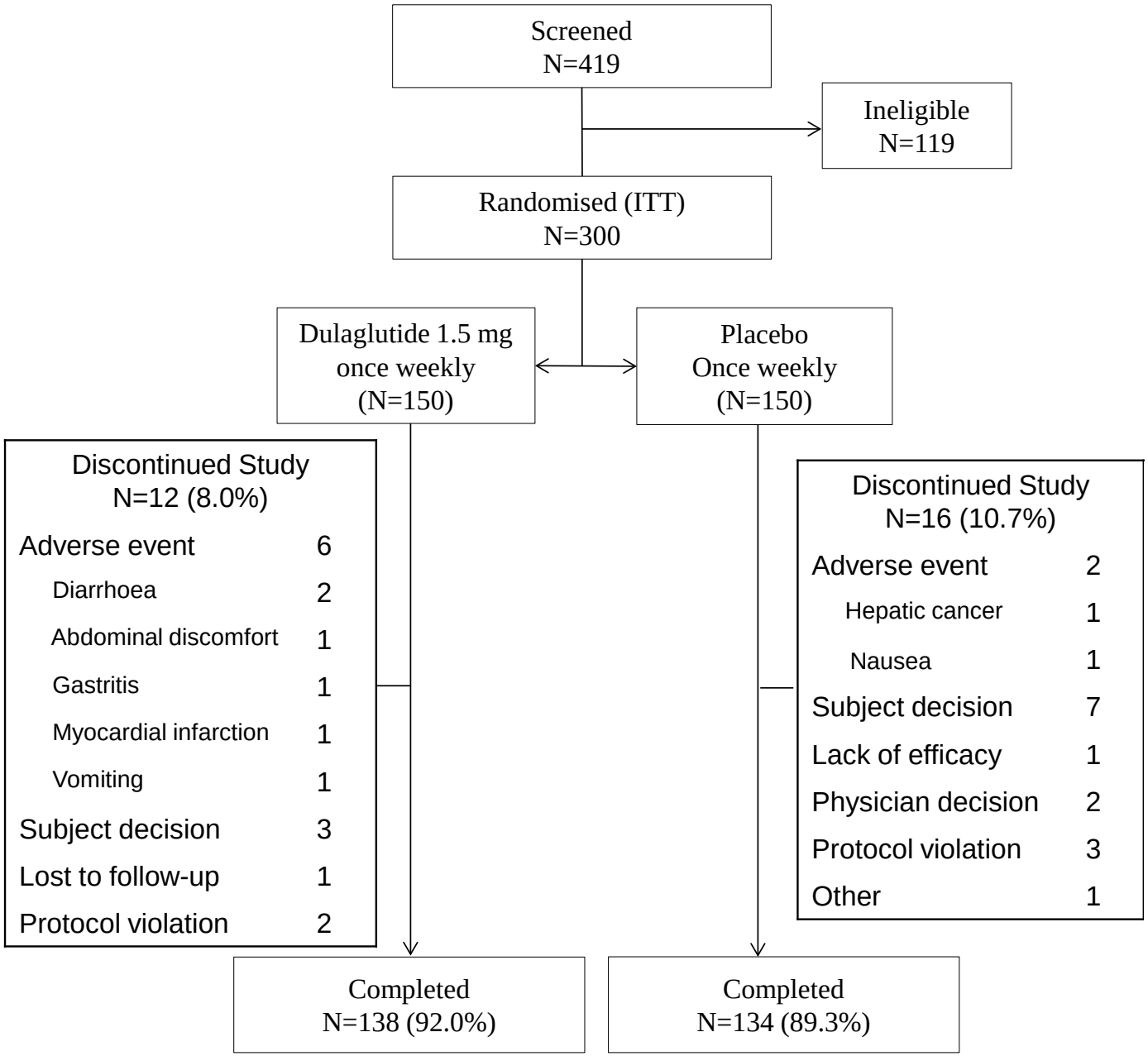
AWARD-9 Study Design



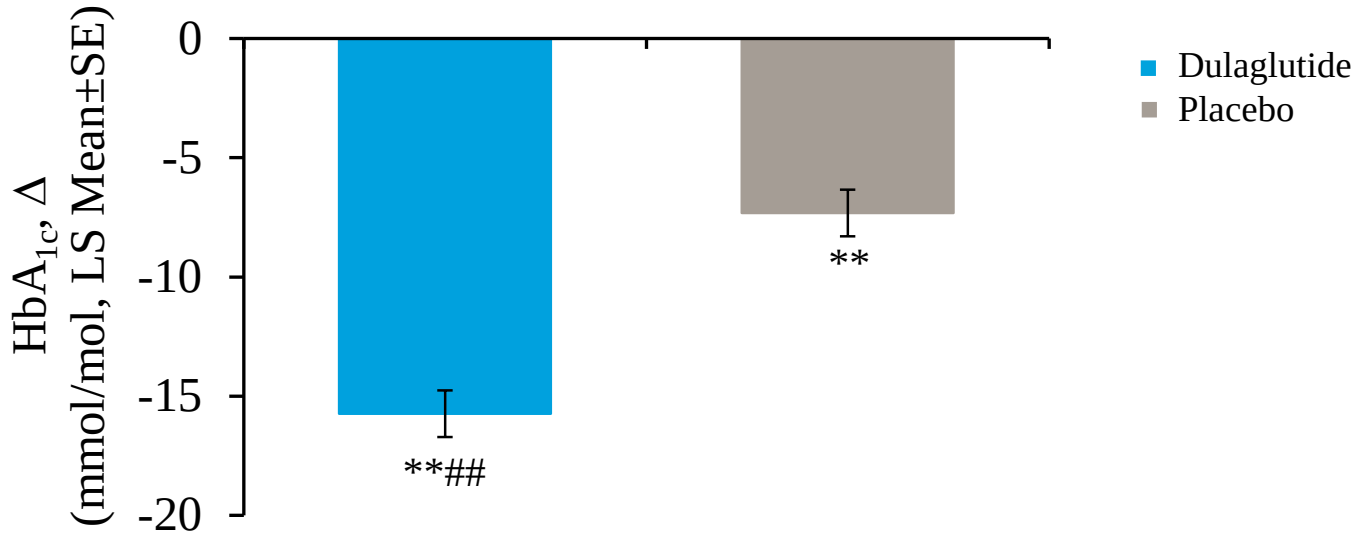
[a]Patients were to continue their pre-study regimen and were not to change the type of antihyperglycaemia medications used or their doses, except when allowed per protocol

[b]At Weeks 7 and 9 (Visits 8 and 10), study sites were to contact patients by telephone and perform procedures per the Study Schedule. Stabilization Period = first 4 weeks after randomization, with restricted insulin dose adjustments. Glargine Titration Period = Weeks 4 to 28 (end of treatment/end of study), with unrestricted insulin dose adjustments. Maintenance Period = Weeks 12 to 28 (end of treatment/end of study), the period when glargine dose is expected to be stable.

Patient disposition

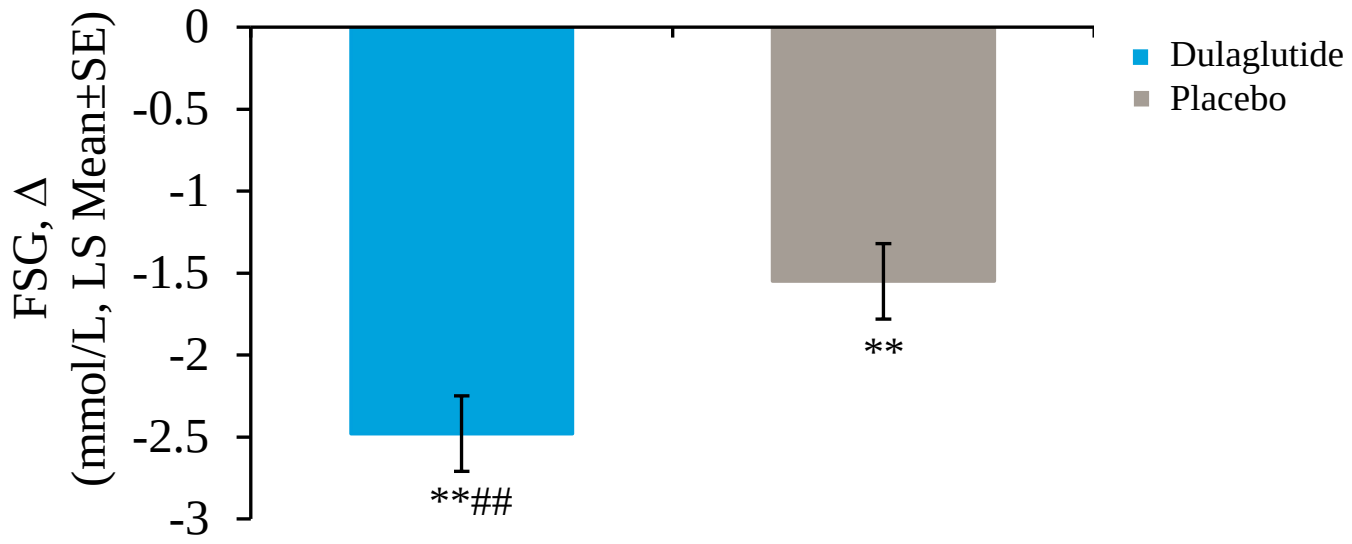


Efficacy of Once Weekly Dulaglutide 1.5 mg versus Placebo, Both Added to Titrated Insulin Glargine, Change in HbA_{1c} from baseline to Week 28 (mmol/mol), MRMM



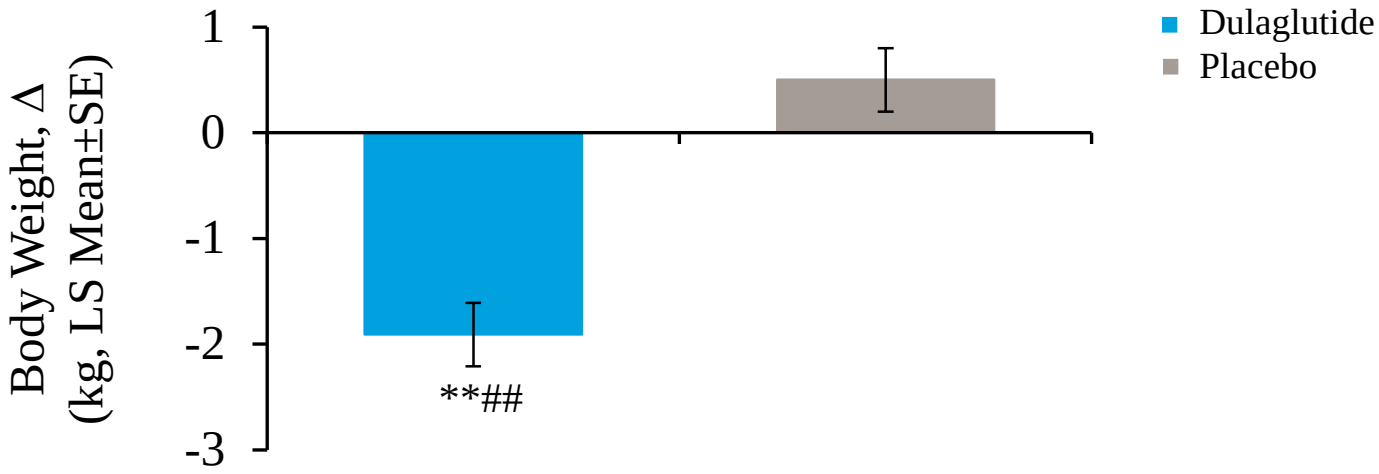
*p<0.05, **p<0.001 change from baseline; #p<0.05, ##p<0.001 dulaglutide versus placebo

Efficacy of Once Weekly Dulaglutide 1.5 mg versus Placebo, Both Added to Titrated Insulin Glargine, Change in Fasting Serum Glucose (FSG) Concentrations from Baseline to Week 28 as Measured by a Central Laboratory (mmol/L), MRMM



*p<0.05, **p<0.001 change from baseline; #p<0.05, ##p<0.001 dulaglutide versus placebo

Efficacy of Once Weekly Dulaglutide 1.5 mg versus Placebo, Both Added to Titrated Insulin Glargine, Change in Body Weight from Baseline to 28 Weeks (kg), MRMM



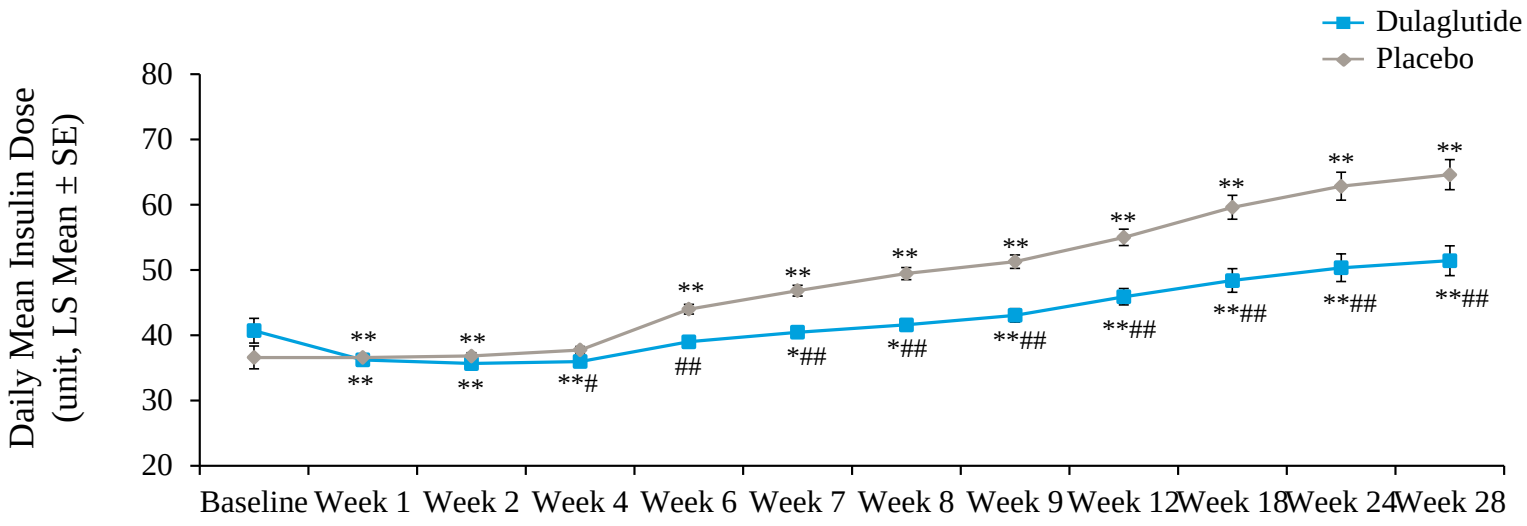
*p<0.05, **p<0.001 change from baseline; #p<0.05, ##p<0.001 dulaglutide versus placebo

Summary and Analysis of Overall Incidence and Rate of Hypoglycaemia (≤3.9 mmol/L) through 28 Weeks

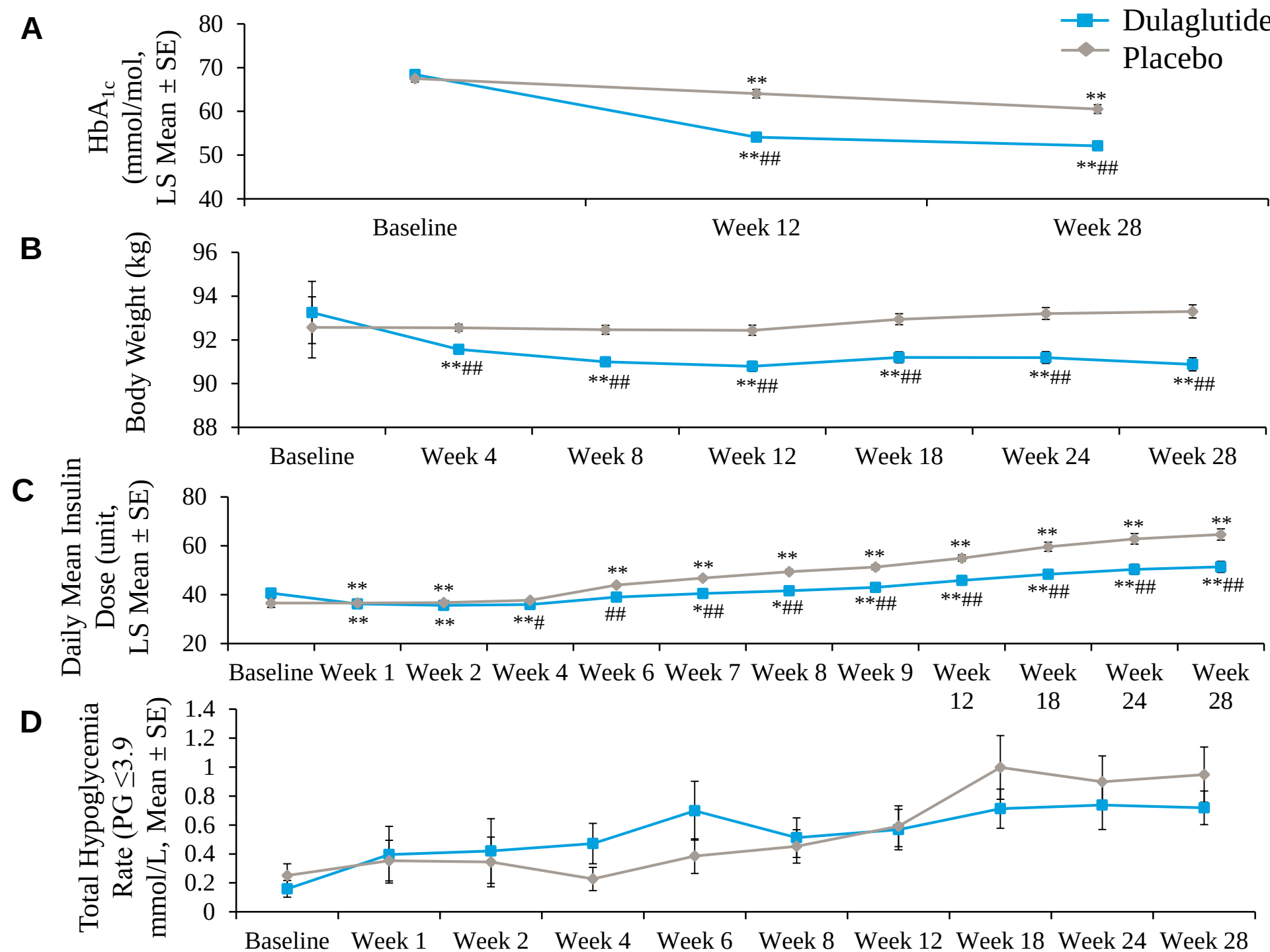
Variable	Dulaglutide 1.5 mg Once weekly (N=150)	Placebo Once weekly (N=150)
Total Hypoglycaemia		
Incidence	82 (54.7)	76 (50.7)
Episodes, n	601	646
Mean Rate (episodes/patient-year)	7.69 ± 15.15	8.56 ± 16.13
Documented Symptomatic Hypoglycaemia		
Incidence	53 (35.3)	45 (30.0)
Episodes, n	269	354
Mean Rate (episodes/patient-year)	3.38 ± 8.62	4.38 ± 11.70
Nocturnal Hypoglycaemia		
Incidence	42 (28.0)	43 (28.7)
Episodes, n	216	234
Mean Rate (episodes/patient-year)	2.76 ± 7.92	3.03 ± 8.96
Diurnal Hypoglycaemia		
Incidence	68 (45.3)	63 (42.0)
Episodes, n	385	412
Mean Rate (episodes/patient-year)	4.93 ± 10.02	5.53 ± 11.59
Severe Hypoglycaemia		
Incidence	1 (0.7)	0 (0.0)
Episodes, n	1	0
Mean Rate (episodes/patient-year)	0.01 ± 0.15	0 ± 0.0

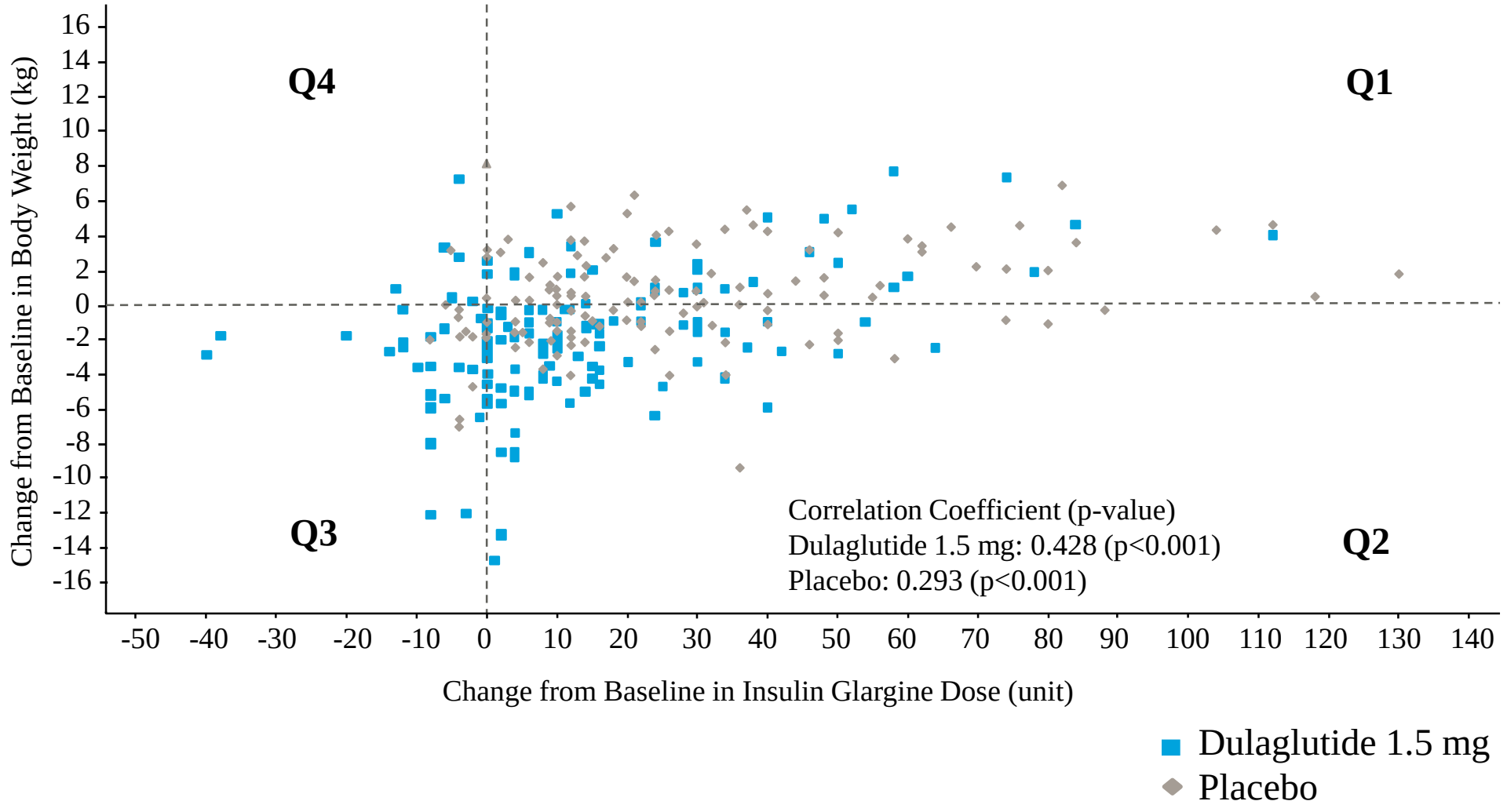
Data is presented as n (%) or mean ± SD. Definitions for hypoglycaemia are provided in the Methods section and supplementary appendix. All p-values were not significant

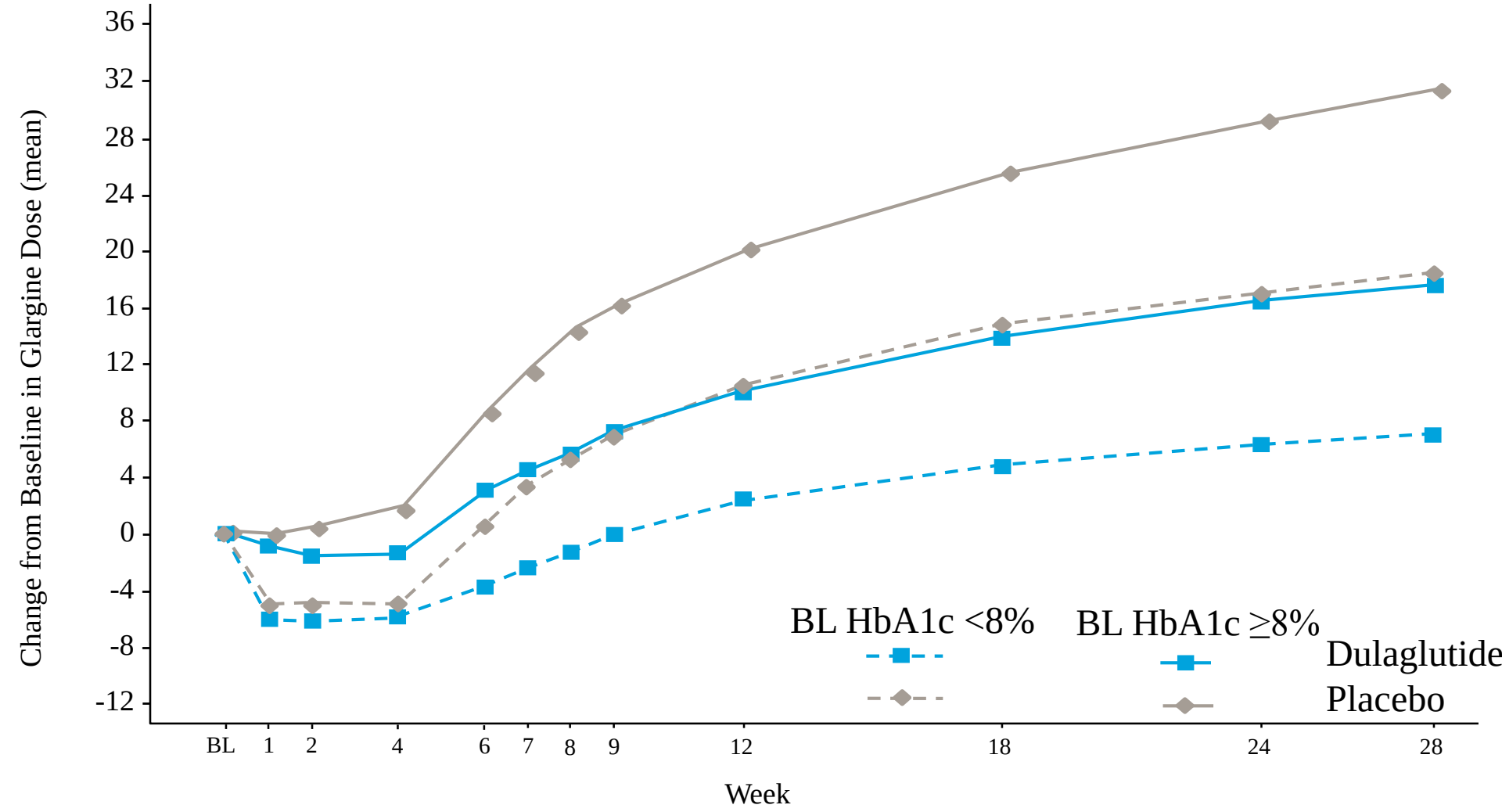
Efficacy and Safety of Once Weekly Dulaglutide 1.5 mg Versus Placebo, Both Added to Titrated Insulin Glargine Over Time, Daily Mean Insulin Glargine Dose (Units), MMRM



*p<0.05, **p<0.001 change from baseline; #*p<0.05, ##**p<0.001 dulaglutide versus placebo


A
B
C
D
Dulaglutide
Placebo
HbA1c (mmol/mol, LS Mean ± SE)
Body Weight (kg)
Daily Mean Insulin Dose (unit, LS Mean ± SE)
Total Hypoglycemia Rate (PG ≤3.9 mmol/L, Mean ± SE)
Baseline
Week 1
Week 2
Week 4
Week 6
Week 7
Week 8
Week 9
Week 12
Week 18
Week 24
Week 28


Q4
Q1
Q3
Q2
Correlation Coefficient (p-value)
Dulaglutide 1.5 mg: 0.428 (p<0.001)
Placebo: 0.293 (p<0.001)
Change from Baseline in Body Weight (kg)
16
14
12
10
8
6
4
2
0
-2
-4
-6
-8
-10
-12
-14
-16
-50
-40
-30
-20
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
Change from Baseline in Insulin Glargine Dose (unit)
Dulaglutide 1.5 mg
Placebo


Change from Baseline in Glargine Dose (mean)
36
32
28
24
20
16
12
8
4
0
-4
-8
-12
BL
1
2
4
6
7
8
9
12
18
24
28
Week
BL HbA1c <8%
BL HbA1c ≥8%
Dulaglutide
Placebo

Supplemental Table 1. Insulin Glargine Dose Titration Algorithm

If median FPG is:	Adjust insulin glargine dose by:
≤3.9 mmol/L	Decrease by 2-4 units[a]
4.0-5.5 mmol/L	No adjustment
5.6-6.6 mmol/L	Increase by 2 units
6.7-7.7 mmol/L	Increase by 4 units
7.8-9.9 mmol/L	Increase by 6 units
≥10 mmol/L	Increase by 8 units

Decisions to adjust insulin doses were based upon the median of the last 3 daily FPG (SMPG) values collected after the previous dose assessment. Abbreviation: FPG = fasting plasma glucose.

[a](A) Dose was also to be decreased by 2-4 units in the following situations: if multiple episodes of nonsevere hypoglycaemia were recorded during the assessment period at any time during the day; and/or if at least 1 episode that met the criteria for severe hypoglycaemia (events requiring assistance to administer therapy) or was associated with self-monitored plasma glucose (SMPG) value <3.0 mmol/L was recorded during the assessment period (B) If only one hypoglycaemic episode with SMPG value ≥3.0 mmol/L and ≤3.9 mmol/L was recorded, insulin dose was not to be changed. Adapted from Riddle, et al. 2003 [1].

Supplemental Table 2. Summary of Self-Monitored Plasma Glucose at Week 12 and Week 28 (mmol/L)

Variable	Dulaglutide 1.5 mg Once weekly (N=150)		Placebo Once weekly (N=150)	
	Week 12	Week 28	Week 12	Week 28
Pre-morning meal	6.02 ± 1.20 (-2.11 [0.16])**$^{\#\#}$	5.66 ± 1.01 (-2.44 [0.15])**$^{\#}$	6.78 ± 1.94 (-1.37 [0.16])**	6.12 ± 1.59 (-1.99 [0.15])**
Post-morning meal	7.96 ± 1.72 (-2.94 [0.25])**$^{\#\#}$	7.27 ± 1.65 (-3.56 [0.24])**$^{\#\#}$	8.94 ± 2.42 (-1.82 [0.24])**	8.25 ± 2.30 (-2.61 [0.24])**
Pre-midday meal	6.76 ± 1.67 (-1.99 [0.21])**$^{\#\#}$	6.45 ± 1.48 (-2.26 [0.21])**$^{\#\#}$	7.96 ± 2.61 (-0.82 [0.21])**	7.32 ± 2.25 (-1.41 [0.20])**
Post-midday meal	8.28 ± 2.06 (-2.48 [0.26])**$^{\#\#}$	7.87 ± 1.71 (-2.84 [0.24])**$^{\#\#}$	9.45 ± 2.64 (-1.22 [0.25])**	8.84 ± 2.35 (-1.83 [0.24])**
Pre-evening meal	7.55 ± 1.73 (-2.16 [0.24])**$^{\#\#}$	7.23 ± 1.76 (-2.42 [0.23])**$^{\#}$	8.81 ± 2.93 (-0.87 [0.23])**	8.03 ± 2.49 (-1.60 [0.23])**
Post-evening meal	8.67 ± 2.21 (-2.43 [0.28])**$^{\#\#}$	8.34 ± 2.08 (-2.70 [0.29])**$^{\#\#}$	9.82 ± 2.79 (-1.27 [0.27])**	9.56 ± 3.14 (-1.51 [0.29])**
Bedtime, 3 AM or 5 hr After Bedtime	6.65 ± 1.80 (-1.76 [0.23])**$^{\#\#}$	6.24 ± 1.60 (-2.20 [0.24])**$^{\#\#}$	7.49 ± 2.54 (-0.93 [0.23])**	7.27 ± 2.60 (-1.12 [0.23])**

Data is presented as actual value mean ± SD (change from baseline LSM [SE]). *p<0.05, **p<0.001 change from baseline; $^{\#}$p<0.05, $^{\#\#}$p<0.001 dulaglutide versus placebo.

Supplemental Table 3. Summary of Combined Outcomes

Achieved HbA_{1c} Level	Dulaglutide 1.5 mg Once weekly (N=150)	Placebo Once weekly (N=150)
<7.0% at 28 weeks without documented symptomatic hypoglycaemia at weeks 12 to 28	78 (52.0)[##]	42 (28.0)
<7.0% without weight gain at 28 weeks without documented symptomatic hypoglycaemia at weeks 12 to 28	61 (40.7)[##]	25 (16.7)
<7.0% without weight gain at 28 weeks, LOCF	79 (52.7)[##]	30 (20.0)

Data are presented as n (%). Without weight gain refers to <0.1 kg. [##] p<0.001 dulaglutide versus placebo. The maintenance period ranged from weeks 12 to 28. Abbreviations: LOCF = last observation carried forward

Supplemental Table 4. Glargine Dose Titration Profile and Fasting Serum Glucose for Patients with Baseline HbA_{1c} Level <8% or ≥8%

Week	n	Baseline	Week 1	Week 2	Week 4	Week 6	Week 7	Week 8	Week 9	Week 12	Week 18	Week 24	Week 28
Insulin dose, U													
DU 1.5 mg with BL HbA_{1c} <8.0%	51	38.8 ± 21.1	32.8 ± 18.5	32.6 ± 18.5	32.9 ± 18.4	35.0 ± 17.1	36.4 ± 17.1	37.5 ± 17.0	38.3 ± 17.1	40.8 ± 18.2	43.2 ± 20.1	44.7 ± 22.8	45.3 ± 24.0
DU 1.5 mg with BL HbA_{1c} ≥8.0%	99	41.7 ± 24.2	40.8 ± 22.1	40.1 ± 21.7	40.4 ± 21.7	44.5 ± 22.7	46.2 ± 23.1	47.4 ± 23.7	48.9 ± 24.1	51.9 ± 25.7	55.7 ± 29.1	58.4 ± 32.8	59.6 ± 34.7
Placebo with BL HbA_{1c} <8.0%	56	31.2 ± 20.4	26.3 ± 16.9	26.5 ± 16.9	26.6 ± 16.7	31.5 ± 17.3	34.2 ± 17.6	36.2 ± 19.2	38.3 ± 20.5	41.8 ± 22.8	45.6 ± 27.4	47.8 ± 30.0	49.4 ± 30.8
Placebo with BL HbA_{1c} ≥8.0%	94	39.8 ± 21.6	39.7 ± 22.2	40.1 ± 23.1	41.6 ± 23.0	48.4 ± 23.9	51.2 ± 24.2	54.1 ± 24.7	55.9 ± 25.5	59.4 ± 26.7	65.3 ± 32.5	68.7 ± 36.5	71.0 ± 38.6
Insulin dose, change from BL, U													
DU 1.5 mg with BL HbA_{1c} <8.0%	51		-6.0 ± 4.8	-6.2 ± 4.7	-5.9 ± 4.8	-3.8 ± 5.9	-2.4 ± 6.4	-1.3 ± 7.4	-0.04 ± 8.3	2.4 ± 10.4	4.8 ± 12.5	6.3 ± 15.5	7.0 ± 16.6
DU 1.5 mg with BL HbA_{1c} ≥8.0%	99		-0.9 ± 4.8	-1.6 ± 7.7	-1.3 ± 8.3	3.0 ± 7.7	4.5 ± 8.6	5.7 ± 10.0	7.2 ± 11.3	10.1 ± 14.4	13.8 ± 18.7	16.3 ± 22.6	17.6 ± 24.7
Placebo with BL HbA_{1c} <8.0%	56		-5.0 ± 5.2	-5.0 ± 5.3	-4.9 ± 5.3	0.6 ± 7.7	3.4 ± 9.1	5.4 ± 9.8	7.0 ± 11.5	10.5 ± 13.9	14.8 ± 17.1	16.9 ± 20.3	18.5 ± 21.6
Placebo with BL HbA_{1c} ≥8.0%	94		-0.1 ± 3.2	0.3 ± 5.0	1.7 ± 5.8	8.5 ± 8.7	11.3 ± 10.1	14.3 ± 11.8	16.1 ± 13.3	20.0 ± 16.4	25.5 ± 22.9	29.1 ± 27.1	31.3 ± 29.3
Fasting serum glucose, mg/dL													
DU 1.5 mg with BL HbA_{1c} <8.0%	51	131.8 ± 32.0								103.8 ± 29.3			96.2 ± 21.3
DU 1.5 mg with BL HbA_{1c} ≥8.0%	99	170.0 ± 49.2								117.9 ± 36.8			108.6 ± 32.3
Placebo with BL HbA_{1c} <8.0%	56	137.7 ± 37.3								119.1 ± 34.7			113.4 ± 33.9
Placebo with BL HbA_{1c} ≥8.0%	94	167.5 ± 49.4								131.4 ± 49.5			125.2 ± 55.1

Data presented as mean ± SD. Abbreviations: BL = baseline; DU = dulaglutide; HbA_{1c} = glycated haemoglobin A_{1c}; U = unit

Supplemental Table 5. Summary and Analysis of Insulin Dose Assessments

Variable	Dulaglutide 1.5 mg Once weekly (N=150)	Placebo Once weekly (N=150)
Subjects with ≥1 insulin dose assessment	145	142
Total number of assessments prior to week 12, mean ± SD	8.0 ± 1.50	8.0 ± 1.49
Number of times assessment was performed correctly	7.5 (92.9)	7.5 (92.3)
Number of times assessment required a dose change	4.9 (60.4)	5.7 (72.1)
Number of times assessment outcome was followed	6.4 (81.3)	6.1 (75.9)
Subjects with insulin dose assessment outcome not followed		
Patient Decision	64 (42.7)	65 (43.3)
Fear of hypoglycaemia	36 (24.0)	37 (24.7)
Inadequate training	6 (4.0)	5 (3.3)
Other	41 (27.3)	39 (26.0)
Investigator Decision	24 (16.0)	28 (18.7)
Risk of hypoglycaemia	17 (11.3)	17 (11.3)
Other	10 (6.7)	18 (12.0)

Data presented as mean number of times at each week in specified category (%) or n (%) unless otherwise noted.

Supplemental Table 6. Summary of Serious Adverse Events by Preferred Term

Variable	Dulaglutide 1.5 mg Once weekly (N=150)	Placebo Once weekly (N=150)
Deaths	0 (0.0)	0 (0.0)
Total serious adverse events	9 (6.0)	7 (4.7)
Angina unstable	1 (0·7)	1 (0.7)
Bradycardia	2 (1.3)	0 (0.0)
Transient ischemic attack	2 (1.3)	0 (0.0)
Atrial fibrillation	0 (0.0)	0 (0.0)
Carotid artery stenosis	1 (0.7)	0 (0.0)
Cerebral infarction	1 (0.7)	0 (0.0)
Coronary artery disease	1 (0.7)	0 (0.0)
Gastroenteritis	1 (0.7)	0 (0.0)
Granulomatous liver disease	1 (0.7)	0 (0.0)
Hepatic cancer	0 (0.0)	1 (0.7)
Hypoglycaemia	1 (0.7)	0 (0.0)
Intervertebral disc protrusion	0 (0.0)	1 (0.7)
Lower limb fracture	1 (0.7)	0 (0.0)
Myocardial infarction	1 (0.7)	0 (0.0)
Non-cardiac chest pain	0 (0.0)	1 (0.7)
Osteoarthritis	0 (0.0)	1 (0.7)
Skin ulcer	0 (0.0)	1 (0.7)
Viral infection	0 (0.0)	1 (0.7)

Data are presented as n (%).

Supplemental Table 7. Summary and Analysis of Overall Incidence and Rate of Hypoglycaemia (≤3.9 mmol/L) through 28 Weeks

Variable	Dulaglutide 1.5 mg Once weekly (N=150)	Placebo Once weekly (N=150)
Total Hypoglycaemia		
Incidence	82 (54.7)	76 (50.7)
Episodes, n	601	646
Mean Rate (episodes/patient-year)	7.69 ± 15.15	8.56 ± 16.13
Documented Symptomatic Hypoglycaemia		
Incidence	53 (35.3)	45 (30.0)
Episodes, n	269	354
Mean Rate (episodes/patient-year)	3.38 ± 8.62	4.38 ± 11.70
Nocturnal Hypoglycaemia		
Incidence	42 (28.0)	43 (28.7)
Episodes, n	216	234
Mean Rate (episodes/patient-year)	2.76 ± 7.92	3.03 ± 8.96
Diurnal Hypoglycaemia		
Incidence	68 (45.3)	63 (42.0)
Episodes, n	385	412
Mean Rate (episodes/patient-year)	4.93 ± 10.02	5.53 ± 11.59
Severe Hypoglycaemia		
Incidence	1 (0.7)	0 (0.0)
Episodes, n	1	0
Mean Rate (episodes/patient-year)	0.01 ± 0.15	0 ± 0.0

Data is presented as n (%) or mean ± SD. Definitions for hypoglycaemia are provided in the Methods section and supplementary appendix. All p-values were not significant