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Research: Treatment

Monotherapy with the once-weekly GLP-1 analogue dulaglutide for 12 weeks in patients with Type 2 diabetes: dose-dependent effects on glycaemic control in a randomized, double-blind, placebo-controlled study

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Abstract

Aims Evaluate dose-dependent effects of once-weekly dulaglutide, a glucagon-like peptide-1 analogue, on glycaemic control in patients with Type 2 diabetes treated with lifestyle measures with or without previous metformin.

Methods This 12-week, double-blind, placebo-controlled, dose–response trial randomized 167 patients who were anti-hyperglycaemic medication-naïve or had discontinued metformin monotherapy [mean baseline HbA_{1c} 59 ± 8 to 61 ± 8 mmol/mol (7.6 ± 0.7 to 7.8 ± 0.8%)] to once-weekly injections of placebo or dulaglutide (0.1, 0.5, 1.0 or 1.5 mg).

Results A significant dose-dependent reduction in HbA_{1c} (least squares mean ± SE) was observed across doses ($P < 0.001$). HbA_{1c} reductions in the 0.5, 1.0 and 1.5 mg dulaglutide groups were greater than in the placebo group [−10 ± 1, −11 ± 1 and −11 ± 1 vs. 0 ± 1 mmol/mol (−0.9 ± 0.1, −1.0 ± 0.1 and −1.0 ± 0.1 vs. 0.0 ± 0.1%), respectively, all $P < 0.001$]. Dose-dependent reductions in fasting plasma glucose were also observed [least squares mean difference (95% CI) ranging from −0.43 (−1.06 to 0.19) mmol/l for dulaglutide 0.1 mg to −1.87 (−2.56 to −1.19) mmol/l for dulaglutide 1.5 mg, $P < 0.001$]. Dose-dependent weight loss was demonstrated across doses ($P = 0.009$), but none of the groups were different from placebo. The most common adverse events were nausea and diarrhoea.

Conclusions The observed dulaglutide dose-dependent reduction in HbA_{1c} and its acceptable safety profile support further clinical development for treatment of Type 2 diabetes.

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Introduction

Glucagon-like peptide-1 (GLP-1) is an incretin hormone that causes increases in glucose-dependent insulin secretion, inhibition of glucagon secretion, slowing of gastric emptying, and increased satiety [1]. Several GLP-1 analogues have been developed or are in development for treatment of Type 2 diabetes [2–7]. Dulaglutide (Dula; LY2189265; Eli Lilly and Company, Indianapolis, IN, USA), a long-acting GLP-1 analogue, consists of two GLP-1 peptides covalently linked by a small peptide to a human IgG4-Fc heavy chain (Fig. 1). The GLP-1 moieties contain amino acid substitutions that protect from inactivation by dipeptidyl peptidase-4 (DPP-4), while the linker peptide maintains the potency of the GLP-1 peptide. The IgG4-Fc is modified by substituting several amino acids to reduce interaction with high-affinity Fc receptors, cytotoxicity and immunogenicity [8]. The large molecule size is expected to limit its renal clearance. The resulting half-life is approximately 4 days and time to peak concentration is 12–72 h [9].

Dose-dependent reductions in fasting plasma glucose, postprandial glucose and HbA_{1c} were previously reported in patients with Type 2 diabetes ($n = 43$) receiving once-weekly dulaglutide (doses ranging from 0.05 to 8 mg) for 5 weeks [9]. The objective of this Phase 2 study was to assess the dose–response relationship with respect to HbA_{1c} across a narrower range of doses and a longer 12-week treatment period.

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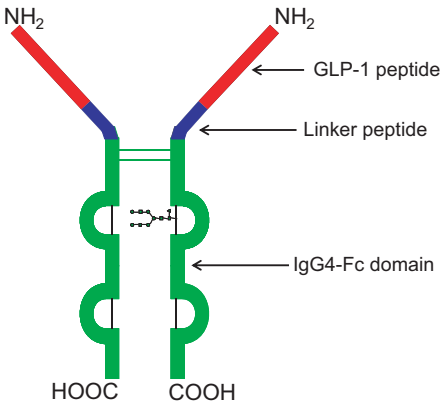

FIGURE 1 Dulaglutide; structure of the molecule.

Research design and methods

Study design

This 12-week, double-blind, placebo-controlled, dose–response study assessed the safety and efficacy of dulaglutide in patients with Type 2 diabetes (n = 167). The study was conducted between November 2008 and January 2010 in 44 sites in seven countries. Eligible patients were anti-hyperglycaemic medication-naïve or on metformin monotherapy. Inclusion criteria were: age ≥ 18 and ≤ 75 years; BMI ≥ 23 to ≤ 40 kg/m^2 for patients native to and residents of South and/or East Asia; ≥ 25 to ≤ 40 kg/m^2 for all other patients; stable weight for 3 months before screening; and HbA_{1c} ≥ 53 to ≤ 80 mmol/mol (≥ 7.0 to ≤ 9.5%) for anti-hyperglycaemic medication-naïve patients and > 48 to ≤ 75 mmol/mol (> 6.5 to ≤ 9.0%) [> 42 to ≤ 69 mmol/mol (> 6.0 to ≤ 8.5%) prior to a protocol amendment] for patients who were taking metformin. Exclusion criteria included treatment with any oral anti-diabetes drug other than metformin within 3 months or other GLP-1 analogue within 6 months prior to screening, prior use of insulin for long-term glycaemic control, serious cardiovascular condition, liver disease, history of pancreatitis or serum creatinine ≥ 1.5 mg/dl (men) or ≥ 1.4 mg/dl (women).

Study periods included: 2-week screening, 4- to 8-week lead-in (8-week washout after discontinuing metformin was required prior to obtaining the qualifying HbA_{1c}); 12-week treatment period; and 4-week safety follow-up. After lead-in, an HbA_{1c} value ≥ 48 to ≤ 80 mmol/mol (≥ 6.5 to ≤ 9.5%) [≥ 53 to ≤ 80 mmol/mol (≥ 7.0 to ≤ 9.5%) prior to protocol amendment] was required for randomization. Patients were randomized (block sizes of 5) to one of five treatment arms: placebo, 0.1 mg, 0.5 mg, 1.0 mg or 1.5 mg dulaglutide (Dula 0.1, Dula 0.5, Dula 1.0 and Dula 1.5) in a 1:1:1:1:1 ratio via an interactive voice-response system. In the original design, patients were randomized to placebo, 0.1 mg, 0.5 mg, 1.0 mg or 3.0 mg dulaglutide. Based on recommendations from the data monitoring committee of another dulaglutide study, the Dula 3.0 arm was discontinued in May 2009 and the protocol was amended to replace the Dula 3.0 arm with the Dula 1.5 arm. A total of 17 patients had been randomized prior to protocol amendment; the three patients on the Dula 3.0 dose were discontinued and the other 14 patients continued on randomized treatment.

Patients were stratified for randomization by country, BMI and pre-study therapy (metformin use or not). Study drug was administered once weekly by subcutaneous injection; as this was a placebo-controlled study, the use of additional oral anti-diabetes drugs was permitted only when needed for rescue therapy (according to pre-specified criteria). If rescued, patients continued to administer the study drug until the last on-treatment visit. Other GLP-1 agonists and DPP-4 inhibitors were not allowed at any time.

A common protocol was approved at each site by an institutional review board and was performed in accordance with the principles of the Declaration of Helsinki. Prior to participation, all patients provided written informed consent.

Study endpoints

The primary efficacy measure was change from baseline in HbA_{1c} at 12 weeks. Additional measures included changes in fasting plasma glucose (central laboratory), 7-point self-monitored plasma glucose, β-cell function and insulin sensitivity using the homeostasis model assessment 2 (HOMA2-%B and HOMA2-%S, respectively), body weight and proportion of patients achieving HbA_{1c} < 53 or ≤ 48 mmol/mol (< 7 or ≤ 6.5%). Safety assessments included cardiovascular (pulse rate, blood pressure, electrocardiogram) and laboratory parameters, reported adverse events and anti-dulaglutide antibodies. Electrocardiograms were recorded in triplicate and tracings were over-read by a cardiologist at a centralized vendor (Biomedical Systems Corporation, Maryland Heights, MO, USA); this report was used for analysis. Referencing the American Diabetes Association definition, 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 an episode requiring the assistance of another person to actively administer therapy [10]. Patients with at least one pancreatic enzyme measurement ≥ 3 times the upper limit of normal underwent a standardized diagnostic examination.

Plasma analytes and HbA_{1c} were quantified by Quintiles Laboratories (Smyrna, GA, USA). Electrochemiluminescence immunosorbent assay was used for detection of anti-dulaglutide antibodies (Millipore, Billerica, MA, USA); positive samples were titrated for titres. Fasting plasma glucose and insulin concentrations were used for HOMA2 calculations [11].

Statistical analysis

The target sample size of 36 patients per group was calculated to provide 90% power for detecting a linear dose–response,

excluding the placebo group, with a 0.60 slope in change from baseline HbA_{1c} for each 1-mg change in dose. Assumptions included residual standard deviation (SD) of 1.2%, 0.61 mg SD of the doses, 2-sided 0.05 significance level and 20% dropout rate. With this sample size, a 0.9% difference in change from baseline in HbA_{1c} could be detected between any dulaglutide group and the placebo group with 80% power.

The primary and secondary analyses were performed on the intention-to-treat population (n = 167), defined as all randomized patients who received study therapy, including patients from the discontinued Dula 3.0 mg arm (n = 3). Changes from baseline were reported as least-squares mean and standard error (least-squares mean ± SE), although summary statistics were not provided for the discontinued Dula 3.0 arm because of the small number.

A mixed-effects model for repeated measures (MMRM) was used for analyses of continuous variables. To evaluate the dose–response relationship on the change in HbA_{1c} at 12 weeks, the model included: country, dose, pre-study therapy (metformin yes/no), visit and dose-by-visit interaction as the fixed effects; baseline BMI and/or baseline HbA_{1c} as a covariate; and patient as a random effect. If baseline BMI and baseline HbA_{1c} were significantly correlated at the 0.10 alpha level, the model included the one that had a higher correlation with the change in HbA_{1c} at 12 weeks. Orthogonal contrasts considering the unequal spacing between doses were used to examine the linear and log linear dose–response without placebo at 12 weeks. The contrast with the smaller SE, representing the better fit, was reported. Dunnett's test was used to control the type I error when comparing placebo to the individual doses.

A Cochran–Armitage trend test was used to assess categorical data, and a one-way ANOVA on the ranks with treatment as a fixed effect was conducted for laboratory data. All statistical analyses were performed using the SAS System® version 8.2 or higher (SAS Institute, Cary, NC, USA).

Results

Patients

In total, 460 patients were screened; most frequent reasons for screen failure were not fulfilling inclusion/exclusion criteria (n = 244), patient decision (n = 36) and physician decision (n = 12). The three patients randomized to Dula 3.0 were discontinued at 1, 64 and 72 days post-randomization; 164 patients were randomized to the other five treatment arms and 153 completed the 12-week treatment (Fig. 2). Twelve patients discontinued before the last safety follow-up visit (Table 1 and Fig. 2). Three patients received rescue therapy (two in the placebo group and one in the Dula 1.0 group). Patient characteristics at entry were well balanced with no significant differences between groups (Table 1).

Primary endpoint

At randomization, baseline HbA_{1c} (mean ± SD) was comparable among groups [60 ± 9, 60 ± 8, 59 ± 8, 61 ± 8 and 60 ± 7 mmol/mol (7.7 ± 0.8, 7.6 ± 0.7, 7.6 ± 0.7, 7.8 ± 0.8 and 7.6 ± 0.7%)] for placebo, Dula 0.1, Dula 0.5, Dula 1.0 and Dula 1.5, respectively (Fig. 3a). Dose-dependent

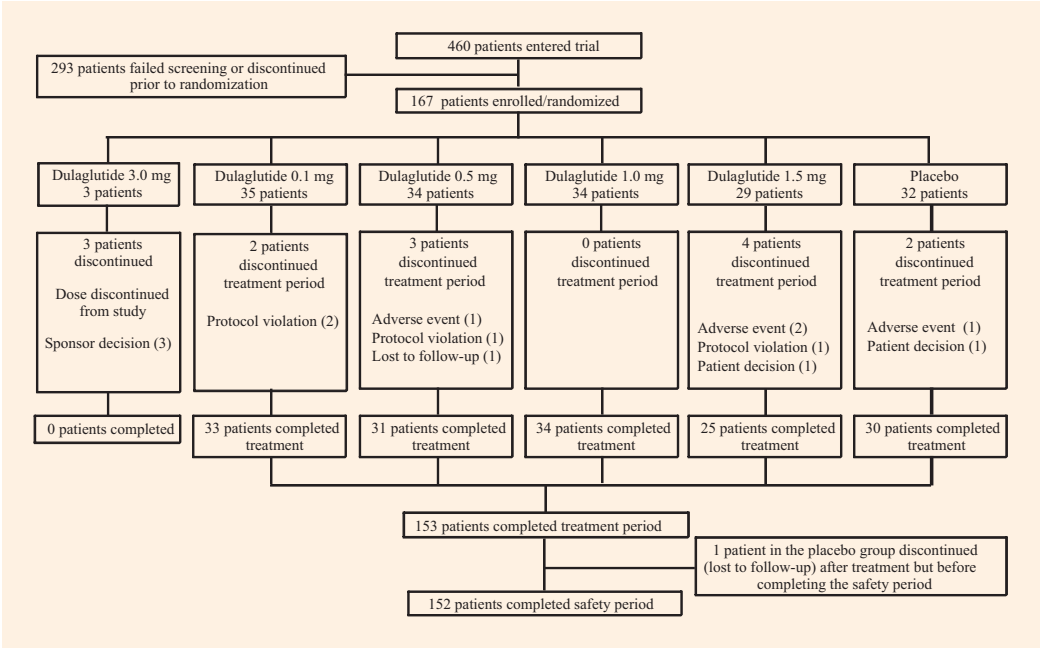

FIGURE 2 Patient disposition from entry to completing safety period throughout the study.

Table 1 Patient characteristics at entry (screening) for intent-to-treat population and reasons for discontinuation

Intent-to-treat population (mean ± SD)	Placebo (n = 32)	Dula 0.1† (n = 35)	Dula 0.5† (n = 34)	Dula 1.0† (n = 34)	Dula 1.5† (n = 29)	Total (n = 164)	P-value*
Age (years)	55.0 ± 9.3	56.3 ± 9.2	56.9 ± 9.1	57.2 ± 8.8	57.5 ± 7.9	56.6 ± 8.8	0.830
Sex							
Female, n (%)	14 (43.8)	24 (68.6)	18 (52.9)	18 (52.9)	16 (55.2)	90 (54.9)	0.360
Male, n (%)	18 (56.3)	11 (31.4)	16 (47.1)	16 (47.1)	13 (44.8)	74 (45.1)	
Race, Caucasian /Asian/Black or African American/Others (%)	78/16/3/3	83/11/3/3	82/15/3/0	77/15/0/9	83/14/3/0	81/14/2/3	0.980
Body weight (kg)	90.9 ± 18.9	87.1 ± 17.3	90.2 ± 21.3	86.9 ± 17.0	85.8 ± 18.6	88.2 ± 18.6	0.770
BMI (kg/m^2)	32.1 ± 5.2	32.9 ± 4.8	32.3 ± 5.4	32.2 ± 4.5	31.0 ± 4.3	32.1 ± 4.8	0.657
HbA_{1c} (mmol/mol)	57 ± 7	54 ± 6	55 ± 7	56 ± 7	56 ± 5	56 ± 6	0.547
HbA_{1c} (%)	7.4 ± 0.6	7.1 ± 0.6	7.2 ± 0.6	7.3 ± 0.7	7.3 ± 0.4	7.2 ± 0.6	
Duration of diabetes (years)	3.9 ± 4.7	3.9 ± 3.2	3.7 ± 3.8	3.3 ± 2.5	4.6 ± 4.1	3.9 ± 3.7	0.722
History of metformin, n (%)							
No	6 (18.8)	7 (20.0)	6 (17.6)	8 (23.5)	4 (13.8)	31 (18.9)	0.912
Yes	26 (81.3)	28 (80.0)	28 (82.4)	26 (76.5)	25 (86.2)	133 (81.1)	
Systolic blood pressure (mmHg)	128.5 ± 12.3	130.7 ± 15.9	129.6 ± 16.1	125.6 ± 15.1	127.3 ± 14.4	128.4 ± 14.8	0.662
Diastolic blood pressure (mmHg)	77.9 ± 10.5	77.1 ± 9.9	75.7 ± 8.9	77.3 ± 9.2	76.8 ± 9.2	77.0 ± 9.5	0.922
Reason for discontinuation, n (%)							
Adverse events	1 (3.1)	0 (0.0)	1 (2.9)	0 (0.0)	2 (6.9)	4 (2.4)	0.254
Lost to follow-up	1 (3.1)	0 (0.0)	1 (2.9)	0 (0.0)	0 (0.0)	2 (1.2)	0.652
Protocol violation	0 (0.0)	2 (5.7)	1 (2.9)	0 (0.0)	1 (3.4)	4 (2.4)	0.562
Subject decision	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)	2 (1.2)	0.265
Completers, n (%)	29 (90.6)	33 (94.3)	31 (91.2)	34 (100)	25 (86.2)	152 (92.7)	0.236

*P-values from analysis of variance or Fisher's exact test.
†0.1 mg, 0.5 mg, 1.0 mg or 1.5 mg dulaglutide.

reductions in HbA_{1c} were observed across the dulaglutide groups ($P < 0.001$) at endpoint. Reductions in HbA_{1c} were greater than placebo for each of the dulaglutide doses ($P < 0.001$) except the Dula 0.1 group ($P = 0.069$); least-squares mean difference (95% CI): Dula 0.1, −4 (−8 to −1) mmol/mol [−0.37 (−0.69 to −0.06) %]; Dula 0.5, −10 (−13 to −6) mmol/mol [−0.89 (−1.21 to −0.57) %]; Dula 1.0, −11 (−15 to −8) mmol/mol [−1.04 (−1.36 to −0.72) %]; and Dula 1.5, −11 (−15 to −8) mmol/mol [−1.04 (−1.39 to −0.70) %] (Fig. 3b); change in the placebo group was least-squares mean ± SE: 0 ± 1 mmol/mol (0.01 ± 0.13%). HbA_{1c} reductions in Dula 0.5, Dula 1.0 and Dula 1.5 were greater than Dula 0.1 ($P \leq 0.001$). There was no difference among the other dulaglutide dose groups.

Secondary endpoints

At endpoint, dose-dependent reductions in mean daily plasma glucose and fasting plasma glucose were observed across all doses ($P < 0.001$) (Fig. 3c and d). Changes in fasting plasma glucose were greater than placebo for each of the doses ($P < 0.001$), except for the Dula 0.1 group ($P = 0.456$); least-squares mean difference (95% CI): Dula 0.1, −0.43 (−1.06 to 0.19) mmol/l; Dula 0.5, −1.47 (−2.12 to −0.83) mmol/l; Dula 1.0, −1.66 (−2.31 to −1.02) mmol/l; and Dula 1.5, −1.87 (−2.56 to −1.19) mmol/l (Fig. 3d); change in the placebo group was least-squares mean ± SE: −0.21 ± 0.25 mmol/l. Dose-dependent reductions in mean pre-meal and postprandial plasma glucose from 7-point self-monitored plasma glucose were observed at endpoint in response to treatment with dulaglutide ($P \leq 0.003$, data not shown). Additionally, decreases in mean pre-meal and postprandial plasma glucose in Dula 0.5, Dula 1.0 and Dula 1.5 groups were significantly greater than placebo (data not shown).

There was an increasing trend across groups in the per cent of patients achieving HbA_{1c} < 53 mmol/mol (< 7.0%) at endpoint ($P < 0.001$): placebo (21%), Dula 0.1 (47%), Dula 0.5 (73%), Dula 1.0 (75%) and Dula 1.5 (71%). There was also an increasing trend in the per cent of patients achieving $HbA_{1c} \leq 48$ mmol/mol (≤ 6.5%) ($P < 0.001$): pla-

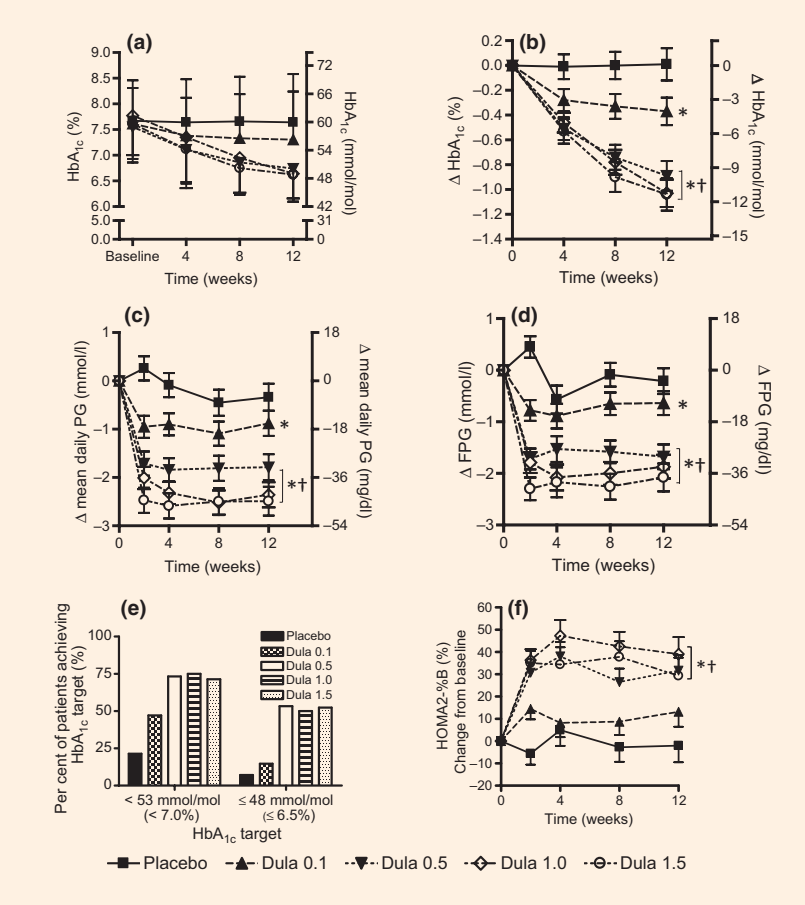

FIGURE 3 Glycaemic control in patients with Type 2 diabetes (intent-to-treat population, n = 164) in response to treatment with placebo (n = 32), Dula 0.1 (n = 35), Dula 0.5 (n = 34), Dula 1.0 (n = 34) or Dula 1.5 mg (n = 29): (a) HbA_{1c} by study visit (mean ± sd); (b) least-squares mean change from baseline in HbA_{1c} by study visit (least-squares mean ± SE); (c) least-squares mean change from baseline in mean daily plasma glucose (PG) from 7-point self monitored plasma glucose (7-point SMPG) profile by visit; (d) least-squares mean change from baseline in fasting plasma glucose (FPG) by study visit; (e) percentage of patients achieving HbA_{1c} targets of < 53 mmol/mol (< 7.0%) and ≤ 48 mmol/mol (≤ 6.5%) at week 12. Statistically significant dose effect is observed for both targets, $P < 0.001$ by Cochran–Armitage trend exact test; and (f) least-squares mean change in HOMA2-%B by visit. Glucose values in mg/dl were converted to mmol/l by dividing by 18. *$P < 0.05$ vs. baseline; †$P < 0.05$ vs. placebo.

cebo (7%), Dula 0.1 (15%), Dula 0.5 (53%), Dula 1.0 (50%) and Dula 1.5 (52%) (Fig. 3e).

At week 12, dose-dependent increases in the homeostasis model assessment of β-cell function (HOMA2-%B) were observed across the dulaglutide groups (P = 0.036). Increases were larger in each of the dulaglutide dose groups ($P \leq 0.013$) except the Dula 0.1 group (P = 0.325) compared with placebo; least-squares mean difference (95% CI): Dula 0.1, 15.2 (−3.8 to 34.3) %; Dula 0.5, 33.7 (14.2 to 53.2) %; Dula 1.0, 41.1 (20.6 to 61.6) %; and Dula 1.5, 31.4 (10.4 to 52.3) %; change in the placebo group (least-squares mean ± SE) was −2.1 ± 7.4%; (Fig. 3f). No significant changes were observed in any dulaglutide group for HOMA2-%S.

Changes in body weight at week 12 (least-squares mean ± SE) were −1.4 ± 0.5 kg for placebo, −0.2 ± 0.4 kg for Dula 0.1, −0.3 ± 0.4 kg for Dula 0.5, −1.1 ± 0.4 kg for Dula 1.0 and −1.5 ± 0.5 kg for Dula 1.5. Dose-dependent reductions in body weight were observed across the dulaglutide groups at week 12 (P = 0.009), but were not significant when compared with placebo. This outcome may be partially related to two patients in the placebo group who experienced weight loss of 11.2 and 11.3 kg as a result of haemorrhagic pancreatitis and participation in a weight-loss programme, respectively.

Safety and tolerability

Overall, 51.8% (n = 85) of patients reported ≥ 1 treatment-emergent adverse event during the treatment period, with no significant trend across groups (see also Supporting Information, Table S1). The most frequent treatment-emergent adverse events were nausea, diarrhoea, and nasopharyngitis, with overall incidences of 7.9% (n = 13), 6.1% (n = 10) and 5.5% (n = 9), respectively; there was no significant trend across

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