Dulaglutide as add-on therapy to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes (AWARD-10): a 24-week, randomised, double-blind, placebo-controlled trial

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Summary

Background Glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose co-transporter-2 (SGLT2) inhibitors improve glycaemic control and reduce bodyweight in patients with type 2 diabetes through different mechanisms. We assessed the safety and efficacy of the addition of the once-weekly GLP-1 receptor agonist dulaglutide to the ongoing treatment regimen in patients whose diabetes is inadequately controlled with SGLT2 inhibitors, with or without metformin.

Methods AWARD-10 was a phase 3b, double-blind, parallel-arm, placebo-controlled, 24-week study done at 40 clinical sites in Austria, Czech Republic, Germany, Hungary, Israel, Mexico, Spain, and the USA. Eligible adult patients (≥18 years) with inadequately controlled type 2 diabetes (HbA_{1c} concentration ≥7·0% [53 mmol/mol] and ≤9·5% [80 mmol/mol]), a BMI of 45 kg/m² or less, and taking stable doses (>3 months) of an SGLT2 inhibitor (with or without metformin) were randomly assigned (1:1:1) via an interactive web-response system to subcutaneous injections of either dulaglutide 1·5 mg, dulaglutide 0·75 mg, or placebo once per week for 24 weeks. Patients and investigators were masked to dulaglutide and placebo assignment, and those assessing outcomes were masked to study drug assignment. The primary objective was to test for the superiority of dulaglutide (1·5 mg or 0·75 mg) versus placebo for change in HbA_{1c} concentration from baseline at 24 weeks. All analyses were done in the intention-to-treat population, defined as all randomly assigned patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT02597049.

Findings Between Dec 7, 2015, and Feb 3, 2017, 424 patients were randomly assigned to dulaglutide 1·5 mg (n=142), dulaglutide 0·75 mg (n=142), and placebo (n=140). One patient in the dulaglutide 0·75 mg group was excluded from the analysis because they did not receive any dose of the study drug. The reduction in HbA_{1c} concentration at 24 weeks was larger in patients receiving dulaglutide (least squares mean [LSM] for dulaglutide 1·5 mg –1·34% [SE 0·06] or –14·7 mmol/mol [0·6]; dulaglutide 0·75 mg –1·21% [0·06] or –13·2 mmol/mol [0·6]) than in patients receiving placebo (–0·54% [0·06] or –5·9 mmol/mol [0·6]; p<0·0001 for both groups *vs* placebo). The LSM differences were –0·79% (95% CI –0·97 to –0·61) or –8·6 mmol/mol (–10·6 to –6·7) for dulaglutide 1·5 mg and –0·66% (–0·84 to –0·49) or –7·2 mmol/mol (–9·2 to –5·4) for dulaglutide 0·75 mg (p<0·0001 for both). Serious adverse events were reported for five (4%) patients in the dulaglutide 1·5 mg group, three (2%) patients in the dulaglutide 0·75 mg group, and five (4%) patients in the placebo group. Treatment-emergent adverse events were more common in patients treated with dulaglutide than in patients who received placebo, mainly because of an increased incidence of gastrointestinal adverse events. Nausea (21 [15%] patients in the dulaglutide 1·5 mg group *vs* seven [5%] in the dulaglutide 0·75 mg group *vs* five [4%] in the placebo group), diarrhoea (eight [6%] *vs* 14 [10%] *vs* four [3%]), and vomiting (five [4%] *vs* four [3%] *vs* one [1%]) were more common with dulaglutide than with placebo. One episode of severe hypoglycaemia was reported in the dulaglutide 0·75 mg group. Two (1%) patients receiving dulaglutide 1·5 mg died, but these deaths were not considered to be related to study drug; no deaths occurred in the other groups.

Interpretation Dulaglutide as add-on treatment to SGLT2 inhibitors (with or without metformin) resulted in significant and clinically relevant improvements in glycaemic control, with acceptable tolerability that is consistent with the established safety profile of dulaglutide.

Funding Eli Lilly and Company.

Introduction

The use of pharmacological drugs as an addition to lifestyle measures is the cornerstone of type 2 diabetes treatment, and most patients need one or more glucose-lowering drugs to achieve glycaemic control targets. The rational use of these medications is based on their stepwise initiation, wherein a new medication class is added to the previously introduced medication class to optimise the efficacy of the treatment regimen while reducing the risk of side-effects.[1] With combination regimens, it is of special interest to investigate the effects of concomitant use of drugs that have complementary

Research in context

Evidence before this study

We searched PubMed on July 18, 2017, using the terms "liraglutide", "exenatide", "albiglutide", "lixisenatide", and "empagliflozin", "dapagliflozin", "canagliflozin", and "randomised controlled trial" and "type 2 diabetes", with no date or trial duration restrictions. Non-English language references were excluded. The search returned 179 publications, two of which included clinical data for the combination of a glucagon-like peptide 1 (GLP-1) receptor agonists and sodium-glucose co-transporter-2 (SGLT2) inhibitor in a controlled clinical study. Fulcher and colleagues reported a post-hoc analysis of the CANVAS trial, in which canagliflozin was added to background GLP-1 receptor agonist therapy, with difference versus placebo reported at 18 weeks. 95 patients were included in the analysis. Placebo-subtracted reductions in HbA$_{1c}$ for canagliflozin 100 mg and 300 mg were –1·00% (95% CI –1·35 to –0·65) and –1·06% (–1·43 to –0·69), respectively, for patients on GLP-1 receptor agonist background therapy. Reductions in bodyweight, plasma glucose, and blood pressure were also reported. Frías and colleagues reported results from a 28-week, phase 3, multicentre, double-blind, randomised, active-controlled clinical trial (DURATION-8), in which 231 patients received exenatide once weekly plus dapagliflozin, 231 received exenatide once weekly alone, and 233 received dapagliflozin alone. Reductions in HbA$_{1c}$ for exenatide plus dapagliflozin were significantly greater from baseline to week 28 compared with exenatide alone (–0·4% [95% CI –0·6 to –0·1]; p=0·004) or dapagliflozin alone (–0·6% [–0·8 to –0·3]; p<0·001). Reductions in bodyweight, plasma glucose, and systolic blood pressure were also greater for exenatide plus dapagliflozin than for other treatments.

Added value of this study

To our knowledge, there are no other reports of phase 3, randomised, controlled clinical trials wherein a GLP-1 receptor agonist has been added to ongoing treatment with stable doses of SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes. In DURATION-8, the GLP-1 receptor agonist (exenatide once weekly) was initiated at the same time as the SGLT2 inhibitor (dapagliflozin), whereas in our study (AWARD-10), we assessed a stepwise treatment strategy as recommended by the American Diabetes Association and the European Association for the Study of Diabetes. Additionally, compared with DURATION-8, in which dapagliflozin was specifically assessed, our study permitted the use of any approved SGLT2 inhibitor and included patients with a lower range of mean baseline HbA$_{1c}$ concentrations who needed a new intervention because the target HbA$_{1c}$ concentration of less than 7·0% (53 mmol/mol) had not been achieved.

Implications from all the available evidence

Our findings show that, compared with placebo, dulaglutide given as add-on treatment to any of the three available SGLT2 inhibitors (with or without metformin) results in significant and clinically relevant improvements in glycaemic control and other outcomes, with acceptable tolerability that is consistent with the established safety profile of dulaglutide. These findings further inform the use of a once weekly GLP-1 receptor agonist in combination with SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes.

actions on the organs and tissues involved in the regulation of carbohydrate metabolism or that might have additive beneficial effects on the risk of macrovascular and microvascular complications. The combination of glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose co-transporter-2 (SGLT2) inhibitors is of particular relevance in this regard because some drugs from these classes have been associated with cardiovascular risk reduction in comparison with standard-of-care regimens.[2–4]

GLP-1 receptor agonists and SGLT2 inhibitors lower plasma glucose concentrations, reduce bodyweight, and bring about other clinically relevant outcomes through different mechanism of actions. GLP-1 receptor agonists enhance insulin secretion in a glucose-dependent manner, inhibit glucagon secretion,[5–15] slow gastric emptying (especially with short-acting drugs), and suppress appetite.[16] Pharmacological inhibition of SGLT2 with SGLT2 inhibitors promotes urinary glucose excretion and indirectly increases glucagon concentration.[17–19] These complementary mechanisms of action suggest that the combination of drugs from these two classes could have additive effects on clinically important outcomes,

including glycaemic control, bodyweight, and blood pressure.

Combination therapy with SGLT2 inhibitors and GLP-1 receptor agonists was not tested during the initial clinical development of SGLT2 inhibitor drugs. In the DURATION-8 trial,[20] Frías and colleagues reported that simultaneous initiation of drugs from these two classes (exenatide once weekly plus dapagliflozin) improved glycaemic control compared with each drug alone and was well tolerated. To the best of our knowledge, the stepwise initiation of GLP-1 receptor agonist in patients receiving stable SGLT2 inhibitor therapy has never been tested. The 24-week Assessment of Weekly AdministRation of LY2189265 (dulaglutide) in Diabetes-10 (AWARD-10) study was designed to assess the efficacy and safety of dulaglutide (1·5 mg or 0·75 mg once weekly) when added to stable doses of an SGLT2 inhibitor (with or without metformin) in patients with inadequately controlled type 2 diabetes. The design of the AWARD-10 study design is in line with the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) recommendation[1,16,21] of a step-wise treatment strategy (add-on to existing therapy) as type 2 diabetes

disease progression warrants the need for additional therapy.

Methods

Study design and participants

AWARD-10 was a 24-week, randomised, phase 3b, double-blind, parallel-arm, placebo-controlled superiority study done at 40 clinical sites in Austria, Czech Republic, Germany, Hungary, Israel, Mexico, Spain, and the USA. The study was completed in accordance with the Declaration of Helsinki, the Council for International Organisations of Medical Sciences International Ethical Guidelines, and the International Conference on Harmonisation Good Clinical Practices Guidelines. The protocol was approved by local institutional review boards. All patients provided written informed consent.

Eligible adult patients (≥18 years) had inadequately controlled type 2 diabetes (HbA_{1c} concentration ≥7·0% [53 mmol/mol] and ≤9·5% [80 mmol/mol]), a BMI of 45 kg/m² or less, and had been taking a commercially available SGLT2 inhibitor with or without metformin (≥1500 mg/day, as tolerated) for at least 3 months. We excluded patients with type 1 diabetes; patients who used any other glucose-lowering drugs (apart from an SGLT2 inhibitor and metformin) 3 months before study entry or between study entry and randomisation; and patients with a serum calcitonin concentration of 20 pg/mL or higher, a history of pancreatitis, an episode of ketoacidosis or hyperosmolar state or coma, a recent cardiovascular event, or active cancer.

Randomisation and masking

Patients were randomly assigned (1:1:1) to subcutaneous injection of dulaglutide 1·5 mg, dulaglutide 0·75 mg, or placebo (all once weekly), stratified for baseline HbA_{1c} concentration, metformin use, and dose of SGLT2 inhibitor (low vs high). Low-dose SGLT2 inhibitor was defined as the lowest dose approved at the time of trial initiation in any of the participating countries (canagliflozin 100 mg, dapagliflozin 5 mg, empagliflozin 10 mg) and high dose was defined as any dose greater than the low dose. Stratification was intended to mitigate baseline heterogeneity between treatment groups.

Randomisation was done by site personnel who accessed the sponsor's interactive web-response system. The system assigned cartons of double-blind study drug for each patient using a computer-generated random sequence. Site personnel were to confirm that they had located the correct cartons by entering a confirmation number found on the carton label into the system.

Procedures

A dose stabilisation period of up to 12 weeks between screening and randomisation was permitted to allow dose adjustments of SGLT2 inhibitors, metformin, or both—for example, when doses were lower than those required according to the study design, or if a dose

reduction was required to comply with local regulatory requirements (eg, decrease in estimated glomerular filtration [eGFR]). Patients continued treatment with the SGLT2 inhibitor with or without metformin after randomisation without changes, except when required per country-specific label. No dose adjustments of injectable study drug (dulaglutide or placebo) were allowed after randomisation.

During the study, new guidelines were published for the adjustment of metformin dosing in response to reductions in eGFR.[22,23] In alignment with these guidelines, patients with subsequent reductions in eGFR were permitted to continue metformin treatment, with appropriate dosing adjustment, within the eGFR range of 31–45 mL/min per m², with discontinuation of metformin at an eGFR of 30 mL/min per m² or less.

Compliance with study drug (dulaglutide or placebo) was determined by review of the patient diary and return of unused study drug at every visit at 2 weeks, 4 weeks, 8 weeks, 12 weeks, 18 weeks, and 24 weeks after randomisation. Patients were considered compliant if at least 75% of study drug doses were administered at each visit interval and for at least 75% of visits attended. Poorly compliant patients received additional training and instructions, as required. Every attempt was made to keep patients in the trial irrespective of their adherence to treatment with study drug to minimise the amount of missing data and to enable assessment of study objectives per the study protocol.[24]

Based on prespecified criteria (appendix), patients who had severe persistent hyperglycaemia or hypoglycaemia between study visits were advised to contact the investigative site. For patients needing rescue therapy for severe persistent hyperglycaemia, other oral antihyperglycaemic drugs or insulin (no GLP-1 receptor agonists) could be added as per published standards of practice.[16,21] For repeated episodes of hypoglycaemia, the metformin dose could be reduced, proceeding to complete withdrawal, as deemed necessary by the investigator. Continued risk of hypoglycaemia, despite discontinuation of metformin, warranted dose reduction or complete withdrawal of the SGLT2 inhibitor. Patients were to continue injectable study drug in either case.

See **Online** for appendix

Outcomes

The primary objective was to test for superiority of dulaglutide relative to placebo for change in HbA_{1c} concentration from baseline to 24 weeks. The key secondary outcomes assessed at 24 weeks were the percentage of patients achieving an HbA_{1c} target concentration of less than 7·0% (53 mmol/mol), change from baseline in bodyweight, and change from baseline in fasting serum glucose concentration. Additional secondary outcomes assessed at 24 weeks were percentage of patients achieving an HbA_{1c} target concentration of 6·5% (48 mmol/mol) or less, six-point self-monitored plasma glucose profile, and change from baseline in fasting glucagon concentration.

Prespecified exploratory measures evaluated at 24 weeks were: the proportion of patients achieving the HbA_{1c} target concentration of less than 7·0% (53 mmol/mol) with no bodyweight gain and no documented symptomatic hypoglycaemia; and the proportion of patients achieving the HbA_{1c} target concentration of less than 7·0% (53 mmol/mol) with bodyweight loss of more than 5% and no documented symptomatic hypoglycaemia.

Adverse events, laboratory parameters, vital signs, and electrocardiograms were assessed for safety. Adverse events of special interest included hypoglycaemia, hyperglycaemia, pancreatitis (abdominal pain, pancreatic enzymes), thyroid safety (serum calcitonin, C-cell hyperplasia, neoplasms), cardiovascular events, renal events, allergic or hypersensitivity reactions, hypotension, urogenital infections, diabetic ketoacidosis, and potentially important gastrointestinal adverse events, such as cholelithiasis or appendicitis. Cases of pancreatitis or cardiovascular events (fatal or non-fatal) were confirmed by independent adjudication. Laboratory measurements were done centrally at time of screening, at time of randomisation, and at 24 weeks (final endpoint) via a central laboratory. A data safety monitoring board was not used in this study; however, masked trial-level safety reviews were done by the study funder.

Hypoglycaemia rate and incidence were recorded as described by Seaquist and colleagues[25] and documented as symptomatic, asymptomatic, probable symptomatic, severe, nocturnal, and total. Additional details about hypoglycaemia are reported in the appendix.

Statistical analysis

We estimated that 120 completers per treatment group would provide 90% power to detect superiority of dulaglutide 1·5 mg or 0·75 mg versus placebo in change in mean HbA_{1c} concentration from baseline to 24 weeks. An SD of 1·2% (13·1 mmol/mol), a difference between dulaglutide and placebo of 0·55% (6·0 mmol/mol), and a 15% dropout rate were assumed; and a two-sided significance level of 0·025 was used in this power calculation.[26]

The primary safety and efficacy analysis population was the intention-to-treat population, defined as all randomly assigned patients who received at least one injected dose of study drug. The primary outcome (change in HbA_{1c}) and the key secondary outcomes were analysed separately on the basis a graphical testing approach[27] to control for type I error, based on the intention-to-treat population, with and without post-rescue data. Details of this approach are provided in the appendix. A mixed-model for repeated measures was used as the primary analysis model. The model included treatment, country, SGLT2 inhibitor dose, metformin use, visit, and treatment-by-visit as fixed effects, and baseline HbA_{1c} concentration as a covariate. We included samples collected at 4 weeks, 12 weeks, and 24 weeks. The mixed-model for repeated measures was used to analyse bodyweight, self-monitored plasma glucose, and vital sign data. Fasting serum glucose and glucagon concentrations were analysed with ANCOVA because only one post-baseline measurement was available. The χ^2 test was used for categorical
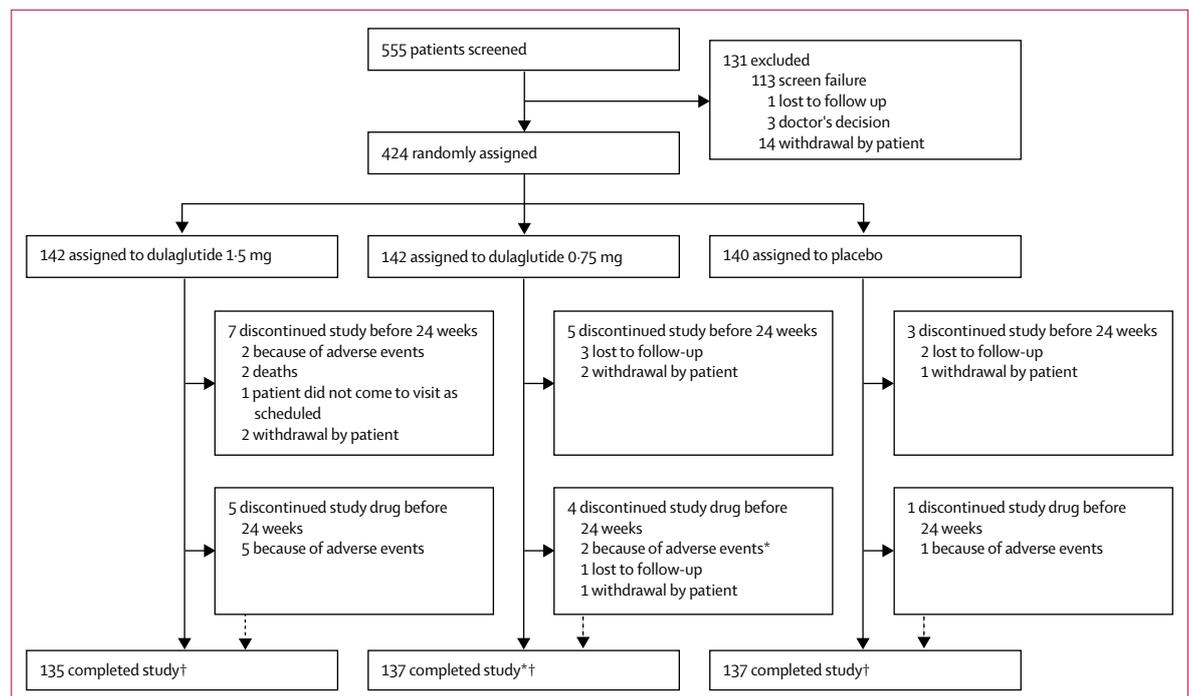

***Figure 1:* Trial profile**
*One patient did not receive any doses of study drug, but completed the study. †Irrespective of duration of exposure to study drug.

measures. The proportions of patients achieving HbA$_{1c}$ target concentrations were analysed using a logistic regression model for repeated measures. Hypoglycaemia rate was analysed using a generalised linear model with negative binomial distribution. All statistical analyses were done with SAS version 9.2.

This trial is registered with ClinicalTrials.gov, number NCT02597049.

Role of the funding source

The funder of the study was involved in study design, data collection, data review, data analysis, data interpretation, and writing of the report. All authors had full access to all the data in the study. BL and JPF had final responsibility for the decision to submit for publication.

Results

Between Dec 7, 2015, and Feb 3, 2017, 424 patients were randomly assigned to receive dulaglutide 1·5 mg (n=142), dulaglutide 0·75 mg (n=142), or placebo (n=140; figure 1). Seven (5%) patients in the dulaglutide 1·5 mg group, five (4%) patients in the dulaglutide 0·75 mg, and three (2%) patients in the placebo group discontinued the study early (figure 1). The most frequent reasons for study discontinuation were adverse events, loss to follow-up, and withdrawal by the patient. Baseline characteristics were similar between treatment groups (table 1). The duration of SGLT2 inhibitor and metformin treatment at time of screening and the mean SGLT2 inhibitor doses at baseline are summarised in the appendix. Across all treatment groups, most patients had taken an SGLT2 inhibitor for 3–6 months; high-dose dapagliflozin (about 10 mg/day) and low-dose empagliflozin (10 mg/day) were the most commonly used SGLT2 inhibitors at screening and study end. The mean doses of the SGLT2 inhibitors and metformin were stable from baseline to study end. 15 patients (two in the dulaglutide 1·5 mg group, three in the dulaglutide 0·75 mg group, and ten in the placebo group) received rescue therapy for hyperglycaemia or an adverse event (appendix). Additionally, eight patients (three in the dulaglutide 1·5 mg group, four in the dulaglutide 0·75 mg group, and one in the placebo group) discontinued study drug early and were retained in the study. One patient in the dulaglutide 0·75 mg did not receive any doses of study drug and was therefore excluded from analysis in the intention-to-treat population.

Changes in HbA$_{1c}$ concentration from baseline to 24 weeks were larger with both dulaglutide doses than with placebo (p<0·0001; figure 2A).

The proportions of patients who achieved the HbA$_{1c}$ target concentrations of less than 7·0% (53 mmol/mol) and 6·5% (48 mmol/mol) or less at 24 weeks was also larger in the dulaglutide groups than in the placebo group (p<0·0001; figure 2B).

Reduction in bodyweight from baseline to 24 weeks was greater with dulaglutide 1·5 mg than with placebo (p=0·028; figure 2C), but the mean bodyweight reduction

in the dulaglutide 0·75 mg group at 24 weeks did not significantly differ from that in the placebo group.

The reduction in fasting serum glucose concentration by 24 weeks was significantly larger with dulaglutide 1·5 mg than with placebo (p<0·0001; figure 2D). Based on the graphical testing scheme, the superiority of dulaglutide 0·75 mg versus placebo for change in fasting serum glucose concentration from baseline to 24 weeks could not be tested.

Both dulaglutide doses reduced self-monitored plasma glucose concentration from baseline to 24 weeks more than placebo did at all six timepoints (figure 3A). The first composite outcome of achieving an HbA$_{1c}$ target less than 7·0% (53 mmol/mol) without weight gain at 24 weeks and without documented symptomatic hypoglycaemia from baseline to 24 weeks was achieved by larger proportions of patients treated with both doses of dulaglutide than in those treated with placebo (both p<0·0001 vs placebo; figure 3B). The second composite outcome of achieving an HbA$_{1c}$ target less than 7·0% (53 mmol/mol) with bodyweight loss more than 5% at 24 weeks and without documented symptomatic hypoglycaemia from baseline to 24 weeks was achieved by

	Dulaglutide 1·5 mg (n=142)	Dulaglutide 0·75 mg (n=141)	Placebo (n=140)
Sex			
Men	77 (54%)	69 (49%)	66 (47%)
Women	65 (46%)	72 (51%)	74 (53%)
Mean age (years)	56·17 (9·26)	58·55 (9·14)	57·10 (9·59)
Aged ≥65 years	23 (16%)	44 (31%)	31 (22%)
Race			
American Indian or Alaska Native	1 (1%)	2 (1%)	4 (3%)
Asian	0	1 (1%)	0
Black or African American	3 (2%)	3 (2%)	6 (4%)
Multiple	11 (8%)	8 (6%)	6 (4%)
White	127 (89%)	127 (90%)	124 (89%)
Ethnic origin			
Hispanic or Latino	51 (36%)	44 (31%)	44 (31%)
Not Hispanic or Latino	90 (63%)	97 (69%)	94 (67%)
Not reported	1 (1%)	0	2 (1%)
Bodyweight (kg)	92·87 (19·73)	91·07 (20·99)	90·50 (19·47)
BMI (kg/m²)	32·87 (5·56)	32·77 (6·27)	32·39 (4·98)
Diabetes duration (years)	9·21 (5·74)	10·05 (6·56)	8·87 (6·13)
HbA$_{1c}$ concentration (%)	8·04 (0·65)	8·04 (0·61)	8·05 (0·66)
HbA$_{1c}$ concentration (mmol/mol)	64·36 (7·11)	64·36 (6·67)	64·47 (7·21)
Fasting serum glucose concentration (mg/dL)	160·65 (33·32)	162·00 (35·75)	153·29 (30·47)
Fasting serum glucose concentration (mmol/L)	8·91 (1·85)	8·99 (1·98)	8·50 (1·69)
Systolic blood pressure (mm Hg)	129·70 (14·48)	130·35 (15·66)	130·57 (13·74)
Diastolic blood pressure (mm Hg)	77·10 (8·96)	76·55 (9·98)	78·36 (9·46)
Treated with metformin	133 (94%)	135 (96%)	135 (96%)

Data are n (%) or mean (SD).
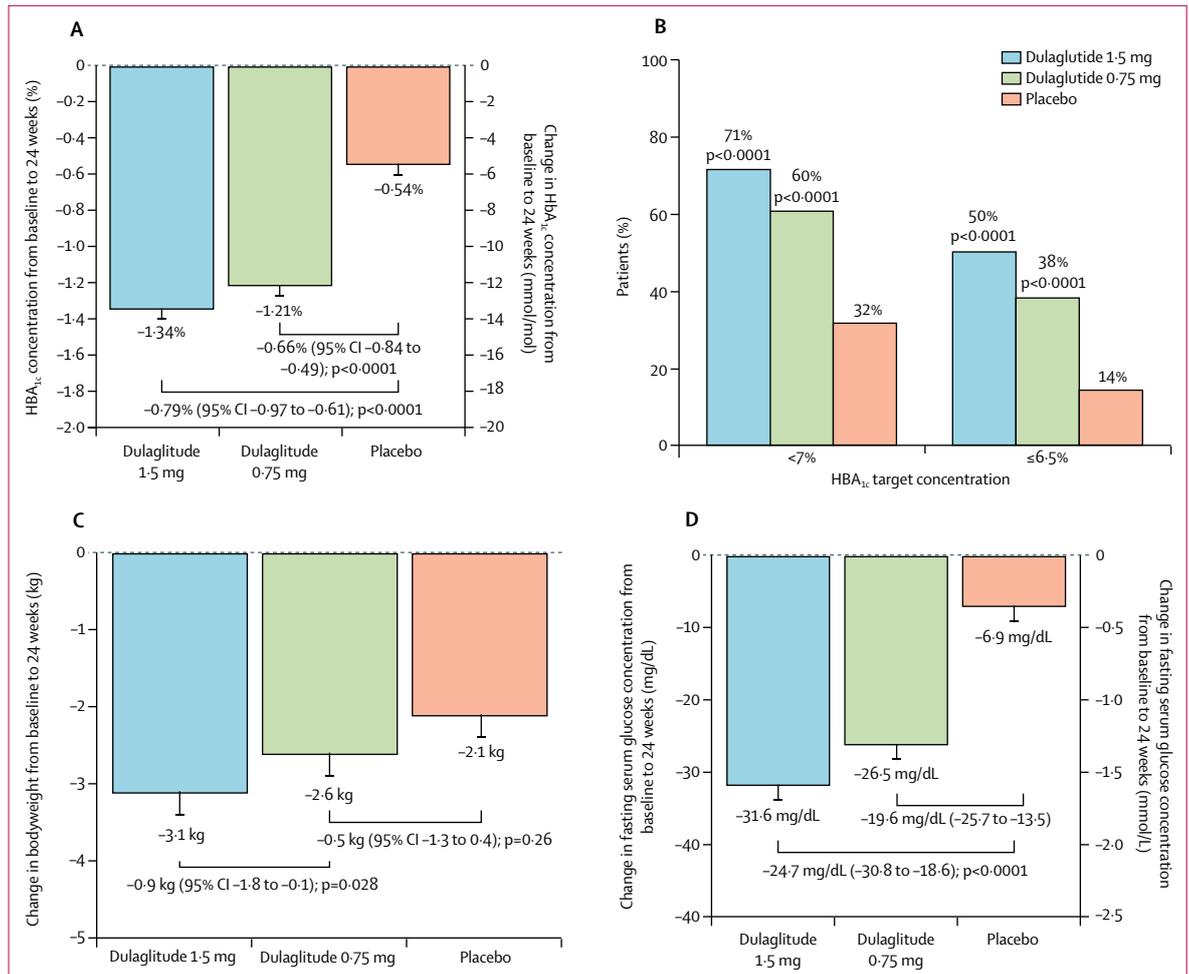
Table 1: Baseline characteristics

***Figure 2:* Efficacy measures**

(A) Change in HbA₁c from baseline to 24 weeks. LSM change: –1·34% (SE 0·06) or –14·7 mmol/mol (0·6) for dulaglutide 1·5 mg; –1·21% (0·06) or –13·2 mmol/mol (0·6) for dulaglutide 0·75 mg; and –0·54% (0·06) or –5·9 mmol/mol (0·6) for placebo. LSM differences for treatment versus placebo at 24 weeks: –0·79% (95% CI –0·97 to –0·61) or –8·6 mmol/mol (–10·6 to –6·7) for dulaglutide 1·5 mg (p<0·0001); and –0·66% (–0·84 to –0·49) or –7·2 mmol/mol (–9·2 to –5·4) for dulaglutide 0·75 mg (p<0·0001). (B) Percentage of patients achieving HbA₁c target concentrations of less than 7·0% (53 mmol/mol) or 6·5% (48 mmol/mol) or less at 24 weeks. (C) Change in bodyweight from baseline to 24 weeks. LSM change: –3·1 kg (SE 0·3) for dulaglutide 1·5 mg; –2·6 kg (0·3) for dulaglutide 0·75 mg; and –2·1 kg (0·3) for placebo. LSM differences for treatment versus placebo at 24 weeks: –0·9 kg (95% CI –1·8 to –0·1; p=0·028) for dulaglutide 1·5 mg; and –0·5 kg (–1·3 to –0·4; p=0·26) for dulaglutide 0·75 mg. (D) Change in fasting serum glucose concentration from baseline to 24 weeks. LSM change: –31·6 mg/dL (SE 2·17) or –1·8 mmol/L (0·12) for dulaglutide 1·5 mg; –26·5 mg/dL (2·2) or –1·5 mmol/L (0·12) for dulaglutide 0·75 mg; and –6·9 mg/dL (2·21) or –0·4 mmol/L (0·12) for placebo. LSM differences for treatment versus placebo at 24 weeks: –24·7 mg/dL (95% CI –30·8 to –18·6) or –1·37 mmol/L (–1·70 to –1·03) for dulaglutide 1·5 mg (p<0·0001); and –19·6 mg/dL (–25·7 to –13·5) or –1·09 mmol/L (–1·43 to –0·75) for dulaglutide 0·75 mg (based on the graphical testing scheme, the superiority of dulaglutide 0·75 mg versus placebo for change in fasting serum glucose concentration from baseline to 24 weeks could not be tested). Error bars show SEs. LSM=least square means.

a larger proportion of patients in the dulaglutide 1·5 mg group than in the placebo group (p=0·035), although the difference between the dulaglutide 0·75 mg group and the placebo group was not significant (p=0·35; figure 3B). The changes in fasting glucagon from baseline are shown in figure 3C. The LSM differences in fasting glucagon of the dulaglutide 1·5 mg and dulaglutide 0·75 mg groups versus placebo at 24 weeks were –1·2 pmol/L (95% CI –2·3 to 0·1; p=0·032) and –0·6 pmol/L (–1·7 to 0·5; p=0·27), respectively (figure 3C).

Results for the intention-to-treat population without data after rescue intervention are summarised in the

appendix. Similar results to those reported above were seen for change in HbA₁c concentration from baseline to 24 weeks and for percentages of patients achieving HbA₁c concentration targets of less than 7·0% (53 mmol/mol) and 6·5% (48 mmol/mol) or less. We found no significant between-group differences in changes in bodyweight from baseline in this analysis. Lack of between-group differences in change of bodyweight from baseline precluded fasting serum glucose superiority testing.

Adverse events are summarised in table 2. Two (1%) patients in the dulaglutide 1·5 mg group died (one uterine carcinoma; one pneumonia); both deaths were determined

by investigators to be unrelated to study drug; no deaths occurred in the other groups. Serious adverse events were reported for five (4%) patients in the dulaglutide 1·5 mg group, three (2%) patients in the dulaglutide 0·75 mg group, and five (4%) patients in the placebo group. Treatment-emergent adverse events were more common in patients treated with dulaglutide than in patients who received placebo. This difference was mainly because of an increased incidence of gastrointestinal adverse events in patients treated with dulaglutide. Nausea, diarrhoea, and vomiting were more common with dulaglutide

treatment than with placebo (21 [15%] patients had nausea in the dulaglutide 1·5 mg group *vs* seven [5%] in the dulaglutide 0·75 mg group *vs* five [4%] in the placebo group; eight [6%] patients had diarrhoea in the dulaglutide 1·5 mg group *vs* 14 [10%] in the dulaglutide 0·75 mg group *vs* four [3%] in the placebo group; and five [4%] patients had vomiting in the dulaglutide 1·5 mg group *vs* four [3%] in the dulaglutide 0·75 mg group *vs* one [1%] in the placebo group). Overall, three fractures (one [1%] patient in each treatment group) and one genital infection (one [1%] patient in the placebo group) were reported,
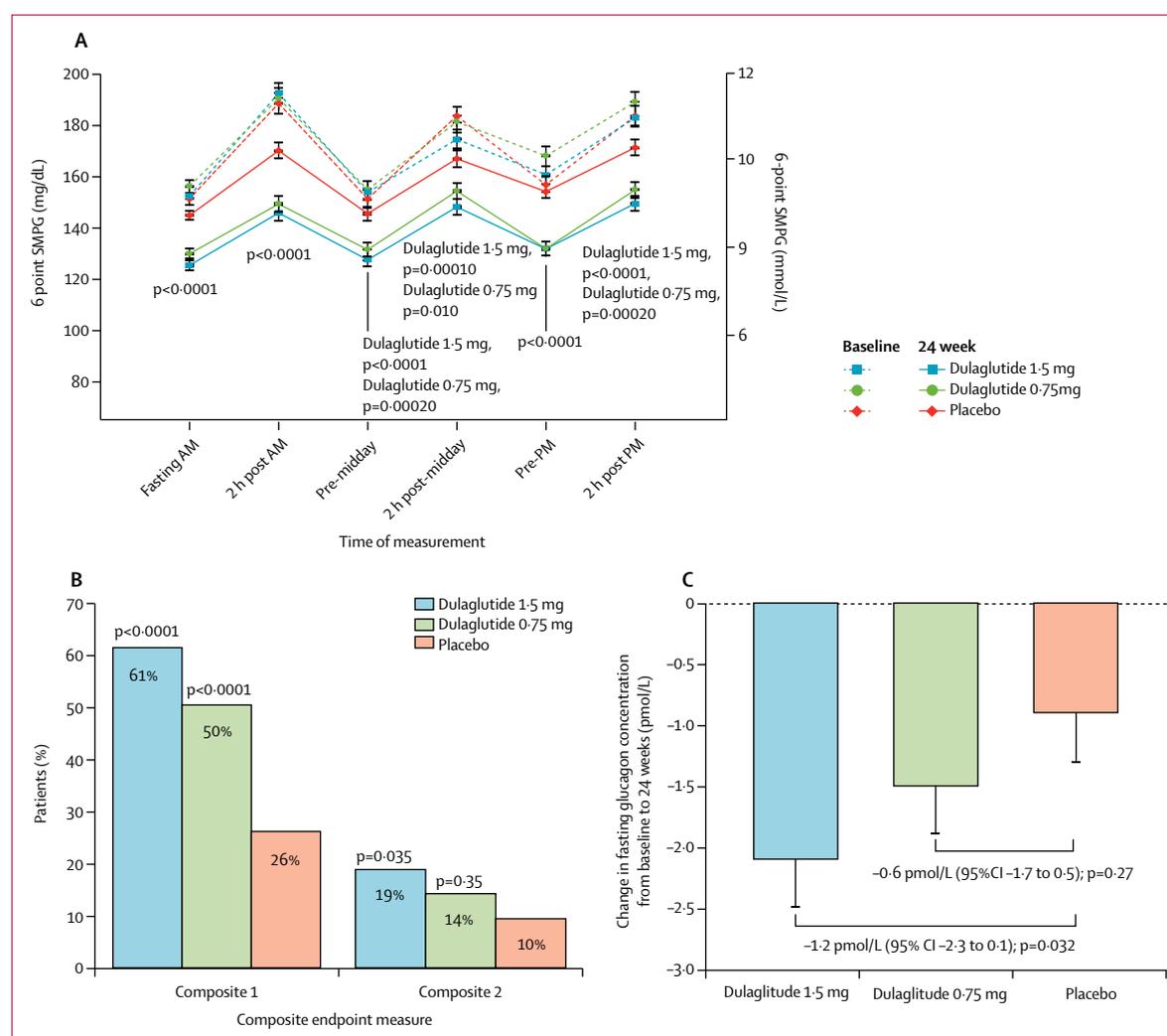

***Figure 3*: SMPG, composite endpoint measures, and fasting glucagon concentration**
(A) Change in SMPG from baseline to 24 weeks. 2 h post AM=2 h after morning meal. Pre-midday=before midday meal. 2 h post-midday=2 h after midday meal. Pre-PM=before evening meal. 2 h post PM=2 h after evening meal. The p values are for both doses of duraglutide versus placebo. At 2 h post-midday, p<0·001 for duraglutide 1·5 mg versus placebo and p<0·05 for duraglutide 0·75 mg versus placebo. (B) Composite endpoint measures. Composite 1 is an HbA$_{1c}$ target less than 7·0% (53 mmol/mol) without bodyweight gain at 24 weeks and without documented symptomatic hypoglycaemia from baseline to 24 weeks. Composite 2 is an HbA$_{1c}$ target concentration of less than 7·0% (53 mmol/mol) with bodyweight loss of more than 5% at 24 weeks and without documented symptomatic hypoglycaemia from baseline to 24 weeks. (C) Changes in fasting glucagon concentration from baseline to 24 weeks. For duraglutide 1·5 mg: LSM change −2·1 pmol/L (SE 0·39); for duraglutide 0·75 mg: −1·5 pmol/L (0·39); for placebo: −0·9 pmol/L (0·40). LSM differences for treatment group versus placebo at 24 weeks were −1·2 pmol/L (95% CI −2·3 to 0·1) for the duraglutide 1·5 mg group (p=0·032) and −0·6 pmol/L (−1·7 to 0·5) for the duraglutide 0·75 mg group (p=0·27). SMPG=self-monitored plasma glucose. LSM=least squares mean.

	Dulaglutide 1·5 mg (n=142)	Dulaglutide 0·75 mg (n=141)	Placebo (n=140)
Deaths	2 (1%)	0	0
Serious adverse events	5 (4%)	3 (2%)	5 (4%)
Adjudication confirmed			
Pancreatic events	0	0	0
Cardiovascular events	0	0	3 (2%)
Cardiovascular death	0	0	0
Non-fatal myocardial infarction	0	0	2 (1%)
Unstable angina	0	0	1 (1%)
Renal and urinary disorders	1 (1%)	3 (2%)	4 (3%)
Treatment-emergent adverse events (patients with ≥1 adverse event)	95 (67%)	83 (59%)	81 (58%)
Treatment-emergent adverse events (≥5% of patients in either group)			
Gastrointestinal disorders	46 (32%)	29 (21%)	24 (17%)
Nausea	21 (15%)	7 (5%)	5 (4%)
Diarrhoea	8 (6%)	14 (10%)	4 (3%)
Other			
Back pain	13 (9%)	12 (9%)	10 (7%)
Headache	8 (6%)	5 (4%)	13 (9%)
Study or study-drug discontinuation, or both, due to adverse events	4 (3%)	0	0
Pancreatic enzymes, LOCF, units per L			
Pancreatic amylase	4·0 (1·0 to 10·0)	4·0 (–1·0 to 8·0)	0·0 (–3·0 to 3·0)
Lipase	7·0 (–3·0 to 16·0)	5·0 (–4·0 to 12·0)	–1·0 (–8·0 to 5·0)
Patients with enzyme concentrations ≥1 × ULN			
Pancreatic amylase	12 (9%)	10 (7%)	6 (4%)
Lipase	29 (20%)	22 (16%)	18 (13%)
Patients with enzyme concentrations ≥3 × ULN			
Pancreatic amylase	1 (1%)	0	0
Lipase	3 (2%)	1 (1%)	1 (1%)
Adverse events of interest associated with SGLT2 inhibitors			
Amputation	0	0	0
Diabetic ketoacidosis	0	0	0
Hypotensive episodes or syncope	0	1 (1%)	1 (1%)
Genital Infections	0	0	1 (1%)
Fractures	1 (1%)	1 (1%)	1 (1%)

Data are n (%) or median (IQR). LOCF=last observation carried forward. SGLT2=sodium-glucose co-transporter-2. ULN=upper limit of normal.

Table 2: Adverse events

Hg [SE 0·63] dulaglutide 1·5 mg group [p=0·93 vs placebo; –0·4 [0·63] dulaglutide 0·75 mg group [p=0·47 vs placebo]; placebo –1·0 mm Hg [0·63]). Increases in heart rate were noted with dulaglutide treatment (LSM change 2·1 beats per min [SE 0·7] for dulaglutide 0·75 mg [p=0·011 vs placebo]; vs 0·6 beats per min [0·7] for dulaglutide 1·5 mg [p=0·31 vs placebo] vs –0·4 beats per min [0·7] for placebo).

Total hypoglycaemia (plasma glucose ≤70 mg/dL [3·9 mmol/L]) between baseline and 24 weeks was reported for five (4%) patients in the dulaglutide 1·5 mg group, five (4%) patients in the dulaglutide 0·75 mg group, and four (3%) patients in the placebo group. 20 events were reported for the dulaglutide 1·5 mg group, 17 events were reported for the dulaglutide 0·75 mg group, and 14 events were reported for the placebo group. No significant between-group differences were identified (p=1·0). The dulaglutide 1·5 mg group had a mean of 0·31 events per patient per year (SD 2·2), compared with 0·26 events per patient per year (1·67) in the dulaglutide 0·75 mg group and 0·21 events per patient per year (1·61) in the placebo group. Documented symptomatic hypoglycaemia occurred at an incidence of 0·16 events per patient per year (1·7) in the dulaglutide 1·5 mg group, at 0·15 events per patient per year (1·3) in the dulaglutide 0·75 mg group, and at 0·12 events per patient per year (1·1) in the placebo group. One episode of severe hypoglycaemia was reported in a patient treated with dulaglutide 0·75 mg.

Changes in pancreatic enzyme concentrations are summarised in table 2. Six patients (five patients in the dulaglutide 1·5 mg group and one in the 0·75 mg group) had pancreatic events of interest, as reported by investigators and submitted for adjudication (five patients had asymptomatic, confirmed increases in the concentration of pancreatic enzymes; one patient had an event of severe abdominal pain without known cause); none were adjudicated as acute or chronic pancreatitis. There were no reports of pancreatic cancer, C-cell hyperplasia, medullary thyroid carcinoma, or cholelithiasis during the study. The incidence of renal adverse events or clinically relevant renal functional variables did not differ between the groups (table 2; appendix).

Six hypersensitivity reactions were reported in four patients: four events were reported in two patients in the dulaglutide 1·5 mg group (two patients had rash, one patient had urticaria, and one patient had an unspecified hypersensitivity reaction); one event was reported in one patient in the dulaglutide 0·75 mg group (urticaria); and one event was reported in one patient in the placebo group (rash). Additionally, one event of injection-site hypersensitivity in the dulaglutide 1·5 mg group was considered a potential immune-mediated injection-site reaction. Overall, 16 (4%) patients (six [4%] in the dulaglutide 1·5 mg group; five [4%] in the dulaglutide 0·75 mg group; and five [4%] in the placebo group) reported one or more treatment-emergent

with no cases of amputation, ketosis, or diabetic ketoacidosis in this study. Four patients (all from the dulaglutide 1·5 mg group) were discontinued from the study because of an adverse event (one abdominal distension, one abdominal pain, one pneumonia, and one uterine carcinoma).

Reductions from baseline in systolic blood pressure were greater for patients in the dulaglutide 1·5 mg group (LSM change –4·5 mm Hg [SE 0·97]) than in the placebo group (–1·4 mmHg [0·97]; p=0·021), but we found no difference between patients in the dulaglutide 0·75 mg group and placebo group (–3·2 mm Hg [0·97]; p=0·17). No differences in diastolic blood pressure were found between dulaglutide and placebo (LSM change –1·1 mm

adverse event identified as possibly related to hypotension: dizziness (n=9); hypotension (n=5); fall (n=3); and syncope (n=2). No renal events or diabetic ketoacidosis were reported.

Discussion

Because of their relatively recent regulatory approvals, combination use of GLP-1 receptor agonists with SGLT2 inhibitors is still not common practice, despite potential advantages over other combinations commonly used to treat patients with type 2 diabetes. In the AWARD-10 trial, addition of once-weekly dulaglutide to ongoing treatment with an SGLT2 inhibitor (with or without metformin) resulted in significant and clinically relevant improvement in HbA_{1c} concentration as compared with placebo. This regimen also resulted in greater reduction of bodyweight with dulaglutide 1·5 mg. Tolerability of dulaglutide was consistent with its known profile when used to treat patients with type 2 diabetes.[26] Improvements in glycaemic control were observed with limited risk of hypoglycaemia and without unexpected adverse events. Although the design of AWARD-10 differed from that of DURATION-8,[20] another randomised trial of GLP-1 receptor agonist and SGLT2 inhibitor co-administration, the results of these two trials suggest multiple potential benefits of this combination in patients with type 2 diabetes.

The current recommended approach to improve glycaemic control while minimising side-effects in the treatment of type 2 diabetes is to individualise therapy to satisfy patient needs, using a clinical strategy that is based on stepwise addition of different classes of glucose-lowering drugs.[16,21] Combination therapy with GLP-1 receptor agonists and SGLT2 inhibitors has received particular interest because these drug classes have complementary effects with respect to glycaemic control. Additionally, findings from several completed studies suggest that drugs from both classes can reduce the risk of cardiovascular events in people at high cardiovascular risk, potentially in part because of effects on bodyweight and blood pressure.[2,3,28] Data describing the effect of adding a GLP-1 receptor agonist to ongoing SGLT2 inhibitor treatment regimens are limited. In one large-scale, randomised clinical trial (DURATION-8),[20] simultaneous initiation of a GLP-1 receptor agonist (exenatide once weekly) and an SGLT2 inhibitor (dapagliflozin) improved glycaemic control, bodyweight, and systolic blood pressure compared with either drug alone in patients with inadequately controlled type 2 diabetes.[20] Similar results were observed when the SGLT2 inhibitor canagliflozin was added to ongoing therapy with a GLP-1 analogue in the the long-term CVOT CANVAS study.[29] Data from retrospective observational studies suggest that GLP-1 receptor agonists and SGLT2 inhibitors are used together off-label in clinical settings for the treatment of type 2 diabetes.[30,31]

We used a study design consistent with the recommendations by the ADA and EASD for the treatment of patients with poorly controlled type 2 diabetes for stepwise introduction of glucose-lowering drugs from different classes. The addition of dulaglutide to ongoing SGLT2 inhibitor treatment (with or without metformin) resulted in clinically relevant glucose-lowering effects, as measured by change from baseline in HbA_{1c} concentration at 24 weeks, and a substantial increase in number of patients reaching the standard treatment target of an HbA_{1c} concentration less than 7·0% (53 mmol/mol). This outcome suggests that the glucose-lowering efficacy of dulaglutide is preserved when initiated in patients treated with SGLT2 inhibitors under conditions of inadequate glycaemic control. Both dulaglutide doses reduced all plasma glucose values from the six-point daily self-monitored plasma glucose profiles versus placebo, suggesting that the reduction in HbA_{1c} concentration is achieved through improvements in fasting, preprandial, and postprandial plasma glucose control. This observation is consistent with changes in the daily self-monitored plasma glucose profile in patients treated with dulaglutide in previous studies.[5–13] The improvement in glucose control was not associated with an increase in the risk of hypoglycaemia because only one episode of severe hypoglycaemia was reported during this trial, confirming the previous observation of a very low incidence of hypoglycaemia with dulaglutide in combination with non-secretagogues. In the case of hypoglycaemia episodes, the trial design required that patients stop metformin first, since the objective of the trial was to study dulaglutide plus SGLT2 inhibitors in combination. In the real clinical situation, since all three drug classes that patients received are non-secretagogues, any of them could be discontinued to mitigate the risk of new events, taking into account patients' preference, adherence, and clinical response to each of these medications.

Clinically relevant improvement in daily and long-term glucose control with combined use of dulaglutide and SGLT2 inhibitors is important in the context of the differences in mechanisms of actions between GLP-1 receptor agonists and SGLT2 inhibitors—enhancement of insulin secretion and glucagon suppression with GLP-1 receptor agonists versus increased urinary glucose excretion and glucagon stimulation with SGLT2 inhibitors. Understanding the effect on glucagon was of special interest in this study because treatment with SGLT2 inhibitors has been shown to increase glucagon concentrations,[17–19] potentially interfering with glucagon-lowering actions of GLP-1 receptor agonists. Importantly, both dulaglutide doses suppressed serum glucagon secretion, with dulaglutide 1·5 mg achieving a significantly greater reduction from baseline versus placebo, consistent with the reductions in fasting glucagon concentration of similar magnitude reported in other studies of dulaglutide.[7,11] The preserved effect of dulaglutide on glucagon when added to SGLT2 inhibitor treatment might be an important contributor to the overall glucose-lowering potency in this patient

population. This preserved effect is not seen with dipeptidyl peptidase-4 (DPP-4) inhibitors or liraglutide when added to treatment with SGLT2 inhibitors since mean glucagon concentrations remained unchanged.[32,33] This finding is potentially due to the lower potency of DPP-4 inhibitors and liraglutide compared with dulaglutide in the suppression of glucagon secretion.

The reduction in HbA_{1c} and bodyweight with dulaglutide 1·5 mg in our study (about 1 kg of additional decrease *vs* placebo) was statistically significant in all analyses apart from the mixed-model for repeated measures without data collected after the initiation of rescue intervention. The estimated absolute reduction in bodyweight was 3·1 kg in the dulaglutide 1·5 mg group in AWARD-10; in the DURATION-8 trial, simultaneous introduction of exenatide once weekly and dapagliflozin resulted in a bodyweight reduction of 3·4 kg.[20]

It is noteworthy that the reduction in HbA_{1c} concentration and bodyweight of patients assigned to placebo in AWARD-10 was larger than expected. One possible reason could be related to the late introduction of SGLT2 inhibitor therapy in many patients (3–6 months before study entry). In other words, continuous decrease in HbA_{1c} and bodyweight in the placebo group after randomisation might suggest that the bodyweight-lowering action of recently introduced SGLT2 inhibitors was ongoing during the treatment period. However, we could not confirm this hypothesis in our assessment of the effect on HbA_{1c} and bodyweight by duration of SGLT2 inhibitor therapy. We have also ruled out a potential effect of rescue interventions that patients received during the treatment period. It is unlikely that metformin therapy had a role since this drug was introduced on average more than 2 years before the study, and doses were stable and unchanged during the trial. Finally, it is not uncommon to see similar decreases in bodyweight and HbA_{1c} concentration without any clear reason (ie, study effect) in clinical trials that include patients with type 2 diabetes.[18,34,35] Although these changes in bodyweight and HbA_{1c} concentration over time in the placebo group might have affected the precise estimate of the contribution of dulaglutide to these outcomes, the trends reported for these measures in the placebo group did not affect our conclusions derived from the study results.

The effect of dulaglutide on glycaemic control, bodyweight, and hypoglycaemia risk translated into a larger proportion of patients treated with dulaglutide who achieved the prespecified composite endpoint of an HbA_{1c} concentration less than 7·0% (53 mmol/mol) without bodyweight gain and without documented symptomatic hypoglycaemia at 24 weeks versus placebo. Composite endpoints are an important tool for assessing how many patients can reach their glycaemic goals without significant patient-relevant side-effects that are often an obstacle in obtaining optimal glucose-lowering outcomes.

Overall, the safety findings were consistent with results of previous studies of dulaglutide in patients with

type 2 diabetes, and no new safety concerns were identified. Similar proportions of patients in all three treatment groups had treatment-emergent adverse events. There were no cases of acute pancreatitis, C-cell hyperplasia, or medullary thyroid cancer during the study. Few patients reported one or more treatment-emergent adverse events that were identified as possibly related to hypotension, a potential concern when two classes of drugs, both of which might cause blood pressure decrease, are combined. No amputations, cases of diabetic ketoacidosis, or acute kidney injury events were reported, and the overall number of urogenital infections was lower than anticipated in a group of patients receiving SGLT2 inhibitors, possibly because of a lower risk in chronically treated patients.

The decrease in systolic blood pressure was larger with dulaglutide 1·5 mg than with placebo, and the change in diastolic blood pressure did not differ between treatment groups. The reduction in systolic blood pressure was consistent with that reported in previous dulaglutide studies. Dulaglutide led to an additional decrease of systolic blood pressure, beyond that observed in the placebo group, suggesting an additive effect of the combination regimen. The reduction in systolic blood pressure, a major cardiovascular risk factor, is of considerable relevance since drugs from the GLP-1 receptor agonist and SGLT2 inhibitor classes have been shown to reduce cardiovascular risk in cardiovascular outcome studies. For example, the GLP-1 receptor agonist liraglutide[2] and the SGLT2 inhibitors empagliflozin and canagliflozin[3,4] were shown to reduce the composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke in patients at high cardiovascular risk. In the DURATION-8 trial, Frías and colleagues[20] showed that concomitant therapy with exenatide once weekly and dapagliflozin resulted in greater improvements in cardiovascular risk factors, including HbA_{1c}, bodyweight, and systolic blood pressure, than did the individual drugs alone, albeit in a population of patients with HbA_{1c} concentration greater than 8% (64 mmol/mol) and lower than 12% (108 mmol/mol). In the present study, we have shown significantly greater improvements in these cardiovascular risk factors when dulaglutide 1·5 mg is added on to stable SGLT2 inhibitor therapy. The ongoing cardiovascular outcome study (REWIND [NCT01394952]) will provide additional information about the cardiovascular effects of dulaglutide in patients with type 2 diabetes.[28]

Limitations of this study include the relatively short duration (24 weeks). A longer study might have provided additional insight into the clinical relevance of concomitant use of dulaglutide and SGLT2 inhibitors. However, guidelines limit placebo-controlled trials to 6 months' duration.[36,37] The trial included patients with inadequate glycaemic control, but with an HbA_{1c} concentration of 9·5% or less, treated with an SGLT2 inhibitor with or without metformin (≥1500 mg per day, as tolerated). The results can therefore not be generalised to patients who do

not meet these criteria. Consistent with regulatory guidance and published standards of care, this study did not include a placebo-only group (all treatment groups received an SGLT2 inhibitor with or without metformin) to inform the contributions of medications to the results observed. Furthermore, we detected a substantial change from baseline for HbA_{1c} concentration in the placebo group. Most patients had been taking an SGLT2 inhibitor for less than 6 months before enrolling in the study, which might partly account for the significant change from baseline in HbA_{1c} concentration and bodyweight in the placebo group.

In conclusion, once-weekly dulaglutide 1·5 mg as add-on treatment to SGLT2 inhibitors with or without metformin resulted in superior glycaemic control, weight loss, reduction in systolic blood pressure, and acceptable tolerability, consistent with the established safety profile of dulaglutide. This combination treatment regimen might be an effective option for the treatment of type 2 diabetes in patients with inadequate glycaemic control.

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