Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial

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Summary

Background Glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose co-transporter-2 (SGLT2) inhibitors reduce glycaemia and weight, and improve cardiovascular risk factors via different mechanisms. We aimed to compare the efficacy and safety of co-initiation of the GLP-1 receptor agonist exenatide and the SGLT2 inhibitor dapagliflozin with exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled by metformin.

Methods DURATION-8 was a 28 week, multicentre, double-blind, randomised, active-controlled phase 3 trial done at 109 sites in six countries. Adults (aged ≥18 years) with type 2 diabetes and inadequate glycaemic control (HbA_{1c} 8–12% [64–108 mmol/mol]) despite stable metformin monotherapy (≥1500 mg/day) were randomly assigned (1:1:1), via an interactive voice and web-response system, to receive once-weekly exenatide 2 mg by subcutaneous injection plus once-daily dapagliflozin 10 mg oral tablets, exenatide with dapagliflozin-matched oral placebo, or dapagliflozin with exenatide-matched placebo injections. Randomisation was stratified by baseline HbA_{1c} (<9·0% *vs* ≥9·0% [<75 mmol/mol *vs* ≥75 mmol/mol]). The primary endpoint was change in HbA_{1c} from baseline to week 28. Secondary endpoints were the change from baseline in fasting plasma glucose at week 2 and week 28, and 2 h postprandial glucose at week 28; the proportion of patients with an HbA_{1c} less than 7·0% (<53 mmol/mol) at week 28; change in weight at week 28; the proportion of patients with weight loss of 5% or more at week 28; and change in systolic blood pressure at week 28. Analyses were by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT02229396.

Findings Between Sept 4, 2014, and Oct 15, 2015, we randomly assigned 695 patients to receive exenatide plus dapagliflozin (n=231), exenatide alone (n=231; n=1 untreated), or dapagliflozin alone (n=233). The intention-to-treat population comprised 685 participants (mean HbA_{1c} 9·3% [SD 1·1]; 78 mmol/mol [12]), of whom 611 (88%) completed the study. After 28 weeks, the change in baseline HbA_{1c} was –2·0% (95% CI –2·1 to –1·8) in the exenatide plus dapagliflozin group, –1·6% (–1·8 to –1·4) in the exenatide group, and –1·4% (–1·6 to –1·2) in the dapagliflozin group. Exenatide plus dapagliflozin significantly reduced HbA_{1c} 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). Exenatide plus dapagliflozin was significantly superior to either drug alone for all secondary efficacy endpoints, with greater reductions in fasting plasma and postprandial glucose, more patients with an HbA_{1c} less than 7·0% (<53 mmol/mol), greater weight loss, a greater proportion of patients with weight loss of 5% or more, and greater reductions in systolic blood pressure (all p≤0·025). Adverse events were recorded in 131 (57%) of 231 patients in the exenatide plus dapagliflozin group, 124 (54%) of 230 patients in the exenatide group, and 121 (52%) of 233 patients in the dapagliflozin group. The most common adverse events (≥5% of patients in any group) were diarrhoea, injection-site nodules, nausea, and urinary tract infections. No episodes of major hypoglycaemia or minor hypoglycaemia were reported.

Interpretation Co-initiation of exenatide and dapagliflozin improved various glycaemic measures and cardiovascular risk factors in patients with type 2 diabetes inadequately controlled by metformin monotherapy. The dual treatment regimen was well tolerated, with the expected safety profile for this combination. Additional data from an ongoing study (eg, AWARD-10; NCT02597049) will further inform the use of these drug classes in combination.

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Introduction

Treatment guidelines recommend initial dual combination therapy for patients with type 2 diabetes who have high HbA_{1c}, with triple combinations recommended if glycaemic control is not achieved after 3 months.[1,2] Although basal insulin is usually included in such combinations, additional treatment choices are needed for patients with high HbA_{1c} who also need to lose weight and avoid hypoglycaemia.

In the past decade, two major classes of glucose-lowering drugs associated with weight loss and a low risk

Research in context

Evidence before this study

We searched PubMed for reports of clinical studies combining a glucagon-like peptide-1 (GLP-1) receptor agonist and a sodium-glucose co-transporter-2 (SGLT2) inhibitor published up to Aug 4, 2016, in any language. Search terms included "type 2 diabetes", class descriptors (sodium-glucose co-transporter-2, SGLT2, glucagon-like peptide-1, GLP-1, glucagon-like peptide-1 receptor agonist, GLP-1RA, and glucagon-like peptide-1 agonist), and terms for individual SGLT2 inhibitors (ASP1941, BI10773, BMS-512148, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, JNJ-28431754, luseogliflozin, LX4211, remogliflozin, TA-7284, and tofogliflozin) and GLP-1 receptor agonists (albenatide, albiglutide, dulaglutide, efpeglenatide, exenatide, liraglutide, lixisenatide, and semaglutide). The search identified 88 publications, only one of which included data for the combined use of a GLP-1 receptor agonist and SGLT2 inhibitors in a controlled clinical study. In this one publication, Fulcher and colleagues reported a post-hoc analysis of a subgroup of 95 patients from the randomised, double-blind, placebo-controlled CANVAS trial, in which the SGLT2 inhibitor canagliflozin was added to background GLP-1 receptor agonist therapy. Placebo-subtracted reductions in HbA_{1c} after 18 weeks of treatment with canagliflozin 100 mg or 300 mg added on to background GLP-1 receptor agonist therapy were –1·00% (95% CI –1·35 to –0·65) with the 100 mg dose and –1·06% (–1·43 to –0·69) with the 300 mg dose. Reductions in fasting plasma glucose, weight, and systolic blood pressure were also reported.

Added value of this study

To the best of our knowledge, DURATION-8 is the first prospective study to investigate the simultaneous addition of a GLP-1 receptor agonist (exenatide) and an SGLT2 inhibitor (dapagliflozin) for treatment of type 2 diabetes in patients with poor glycaemic control despite use of metformin. Our findings show that fixed doses of once-weekly exenatide injections plus once-daily oral dapagliflozin added on to background metformin reduced HbA_{1c} by 2% (22 mmol/mol) in patients with a mean HbA_{1c} of more than 9% (>75 mmol/mol), with greater benefit than addition of either drug alone to metformin. Furthermore, patients receiving the combination therapy had greater weight loss and reductions in fasting plasma and postprandial glucose and systolic blood pressure than did those receiving either drug alone. Exenatide plus dapagliflozin was well tolerated, with a safety profile consistent with that expected for the combination of these therapies, and no episodes of major hypoglycaemia (impairment of consciousness resolving after glucagon or glucose administration, or requiring third-party assistance with blood glucose concentration <3·0 mmol/L [<54 mg/dL]) or minor hypoglycaemia (other symptoms with blood glucose concentration <3·0 mmol/L [<54 mg/dL]) were reported.

Implications of all the available evidence

The findings of this study support the e□cacy and safety of co-initiation of exenatide and dapagliflozin in patients with type 2 diabetes inadequately controlled with metformin monotherapy. Use of once-weekly exenatide and once-daily dapagliflozin in combination could be beneficial in patients with type 2 diabetes with poor glycaemic control, particularly those who wish to lose weight and avoid hypoglycaemia.

of hypoglycaemia have been launched—namely, glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose co-transporter-2 (SGLT2) inhibitors. These drug classes affect glucose metabolism differently, with GLP-1 receptor stimulation increasing insulin secretion, decreasing glucagon secretion, slowing gastric emptying (particularly with short-acting GLP-1 receptor agonists), and increasing satiety, and SGLT2 inhibition increasing urinary glucose excretion.[3–7] These drugs also provide sustained weight loss via different mechanisms, with GLP-1 receptor agonists decreasing food intake by reducing appetite[6] and SGLT2 inhibitors increasing calorie excretion.[8] The glucose-dependent manner of the glucose-lowering mechanisms of these drugs minimises hypoglycaemia risk. In the past year, a drug from each class (liraglutide, a GLP-1 receptor agonist, and empagliflozin, an SGLT2 inhibitor) was shown to significantly reduce cardiovascular events and all-cause mortality compared with standard of care.[9,10]

A recommended treatment approach for patients with type 2 diabetes is combination therapy with glucose-lowering drugs that have shown beneficial effects in clinical trials, and targeting of as many of the pathophysiological defects of the disease as possible (decreased insulin secretion, increased glucagon secretion, increased insulin resistance, neurotransmitter dysfunction, and increased renal glucose absorption) to sustain glycaemic control.[11] Researchers have tested metformin, a thiazolidinedione, and a GLP-1 receptor agonist as initial triple therapy;[12] a thiazolidinedione and a dipeptidyl peptidase-4 (DPP-4) inhibitor as dual therapy added on to metformin;[13] and a DPP-4 inhibitor and an SGLT2 inhibitor as dual therapy added on to metformin.[14] Despite the potential benefits of the combination of a GLP-1 receptor agonist and an SGLT2 inhibitor added on to metformin, this dual add-on combination had not been studied for diabetes in a randomised controlled trial, and therefore could not be included in evidence-based treatment recommendations.

Exenatide—the first-in-class GLP-1 receptor agonist—is administered subcutaneously either twice daily or once weekly (encapsulated in biodegradable microspheres in the once-weekly formulation), whereas dapagliflozin is a first-in-class SGLT2 inhibitor administered orally once

daily.[15,16] Studies of once-weekly exenatide or dapagliflozin have shown glycaemic efficacy, weight loss, low risk of hypoglycaemia, and acceptable tolerability as monotherapy[15,16] or in combination with other glucose-lowering therapies[15,16] for 4 years or longer.[17–19]

We did the DURATION-8 trial to investigate the antihyperglycaemic and metabolic efficacy and safety of co-initiation of treatment with exenatide once weekly and dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin.

Methods

Study design and participants

We did this 28 week, double-blind, parallel-group, randomised, active-controlled phase 3 study at 109 sites in six countries. The study design consisted of a screening visit and a 1 week placebo lead-in before randomisation (appendix). Eligible participants were aged 18 years or older with type 2 diabetes and inadequate glycaemic control (HbA_{1c} 8·0–12·0% [64–108 mmol/mol] inclusive at screening) despite at least 2 months of treatment with a stable dose of metformin (≥1500 mg/day). We excluded patients who received any glucose-lowering drugs other than metformin for more than 14 days in the 12 weeks before enrolment. The appendix provides a complete list of inclusion and exclusion criteria.

The study protocol was approved by institutional review boards and ethics committees at each site. We did the study in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent.

Randomisation and masking

Patients were randomly assigned centrally (1:1:1), via an interactive voice and web-response system, to receive exenatide 2 mg once weekly with dapagliflozin 10 mg once daily (exenatide plus dapagliflozin group), exenatide with once-daily oral placebo tablets (exenatide group), or dapagliflozin with once-weekly injections with placebo microspheres (dapagliflozin group) in addition to their existing metformin regimen. The study did not include a placebo-only group for ethical reasons, based on the inclusion of patients with very high baseline HbA_{1c}. Randomisation was stratified by baseline HbA_{1c} (<9·0% *vs* ≥9·0% [<75 mmol/mol *vs* ≥75 mmol/mol]).

Patients, investigators, and data analysts were masked to treatment assignment. Placebo was supplied as oral tablets matching those of dapagliflozin or as powder along with prefilled syringes of diluent as a suspension for injection matching that provided for exenatide.

Procedures

Diet and exercise instructions were provided as per usual investigator practice. Before the first doses of study drugs, study personnel instructed patients about administration. Participants used a single-dose syringe to self-administer exenatide or matching placebo by subcutaneous injection in the abdomen, thigh, or upper arm at any time of day immediately after dose preparation. We exclusively used single-dose trays of Bydureon (AstraZeneca, West Chester, OH, USA)—the extended-release form of exenatide. Injections were administered once weekly at home or at a study visit (weeks 1, 2, 4, 8, 12, 16, 20, 24, and 28; appendix). Dapagliflozin or matching placebo tablets were likewise self-administered. Patients requiring rescue therapy received open-label titrated basal insulin based on fasting plasma glucose (FPG) criteria: FPG more than 15 mmol/L (270 mg/dL) between weeks 8 and 12; more than 13·2 mmol/L (240 mg/dL) between weeks 12 and 20; and more than 11·1 mmol/L (200 mg/dL) between week 20 and study end. Use of background antihypertensive or antihyperlipidaemic drugs was not restricted.

See Online for appendix

Outcomes

All reported outcomes were prespecified. The primary endpoint was change in HbA_{1c} from baseline to week 28. Secondary glycaemic endpoints were the proportion of patients achieving an HbA_{1c} target of less than 7·0% (<53 mmol/mol) at week 28, change in FPG from baseline to week 2 and week 28, and change in 2 h postprandial glucose from baseline to week 28. Postprandial glucose was measured as part of a standardised meal tolerance test following a liquid meal of defined nutrient content (Ensure Plus [Abbott Nutrition, Abbott Park, IL, USA] or regional equivalent). Exploratory glycaemic endpoints at week 28 were the proportion of patients achieving an HbA_{1c} target of 6·5% or less (≤48 mmol/mol), change in six-point self-monitored blood glucose (SMBG) profiles, and the proportion of patients rescued or discontinued due to poor glycaemic control. No specific diet was requested during the days of SMBG assessments. In a prespecified subgroup analysis, we assessed change in HbA_{1c} from baseline to week 28 by baseline HbA_{1c} (<8%, ≥8% to <9%, and ≥9% [<64, ≥64 to <75, and ≥75 mmol/mol]).

Secondary cardiovascular risk-factor endpoints were changes from baseline to week 28 in weight and systolic blood pressure, and the proportion of patients with weight loss of 5% or more. Exploratory cardiovascular risk-factor endpoints were changes from baseline in diastolic blood pressure, waist circumference, and fasting lipids (total cholesterol, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, and triglycerides). In a prespecified subgroup analysis, we assessed weight change from baseline by baseline HbA_{1c}.

Additional exploratory endpoints were treatment satisfaction and weight-related quality of life, assessed with the Diabetes Treatment Satisfaction Questionnaire, status version (DTSQ-s) and the Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (SHIELD)-WQ-9 questionnaire scores at week 28.

Exploratory endpoints at week 28 to be reported elsewhere are the proportions of patients with an HbA_{1c} reduction of at least 1·0% (10·9 mmol/mol), an HbA_{1c} reduction of at least 1·0% (10·9 mmol/mol) and a weight reduction of at least 3·0%, and with any reduction in both HbA_{1c} and weight; changes in homoeostatic model assessment of β-cell function and insulin sensitivity scores; and change in total bodyweight in patients without an adverse event of nausea. Additional endpoints from meal testing will also be reported. Exploratory post-hoc analyses will be done to further enhance the interpretation and understanding of the primary results.

Safety variables were summarised descriptively and included spontaneously reported adverse events, coded with the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 preferred terms, laboratory tests, including anti-exenatide antibodies, estimated glomerular filtration rate (eGFR), serum creatinine, haematocrit, marked abnormalities of haematocrit (defined as >55%), haemoglobin and uric acid concentrations; and vital signs, including heart rate. Hypoglycaemic episodes were classified as major, minor, or other. Major hypogylcaemia was defined as loss of consciousness, seizure, or coma resolving after glucagon or glucose administration, or any event requiring third-party assistance to resolve because of severe impairment in consciousness or behaviour with a glucose concentration of less than 3·0 mmol/L (<54 mg/dL). Minor hypoglycaemia was defined as a non-major hypoglycaemia event with symptoms consistent with hypoglycaemia and a glucose concentration of less than 3·0 mmol/L (<54 mg/dL) before treatment of the episode. Other hypoglycaemic events were defined as events not meeting the criteria for major or minor hypoglycaemia. Potential cardiovascular or hepatic events were adjudicated by blinded independent cardiology or hepatic adjudication committees by use of prespecified

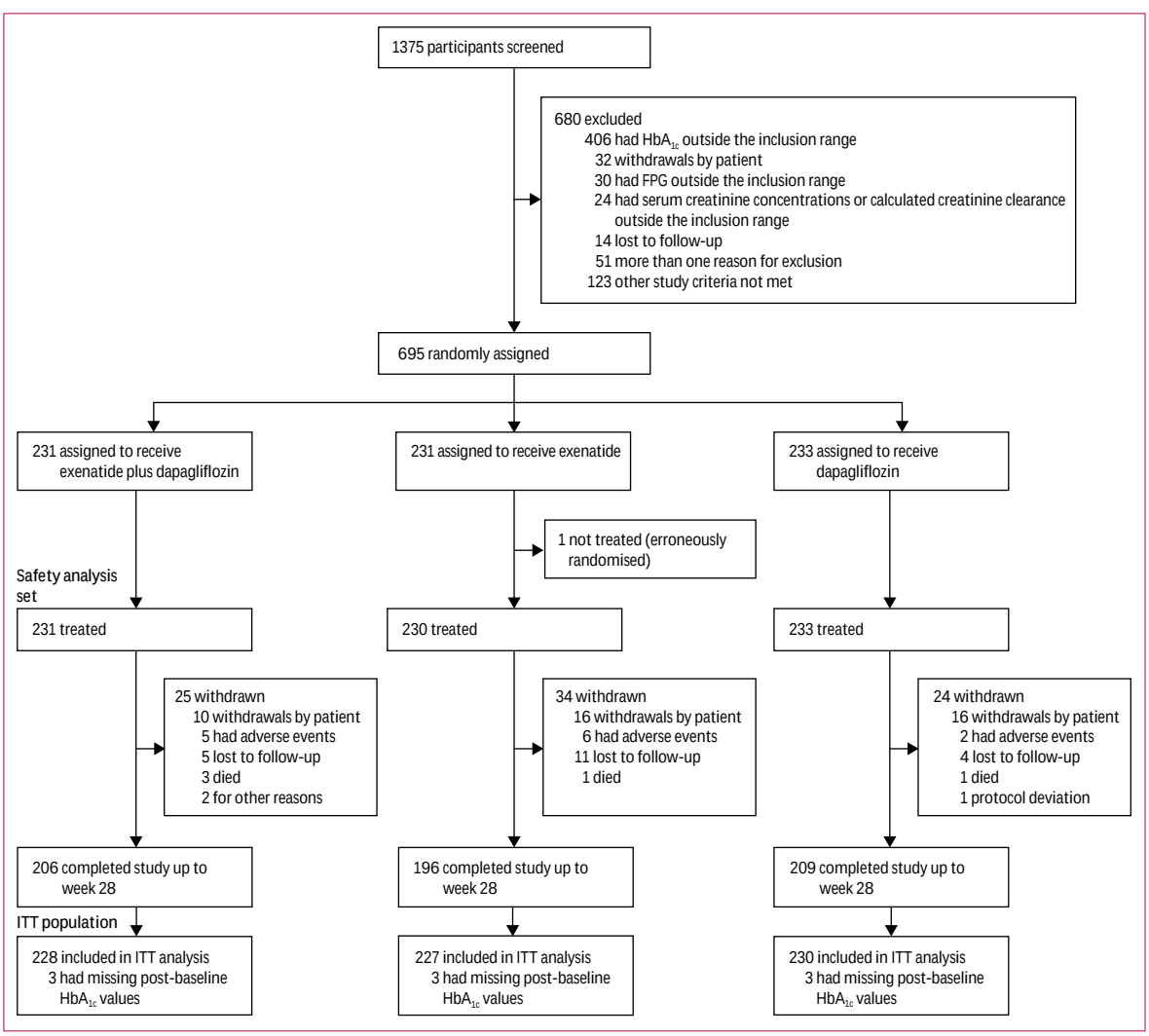

Figure 1: Trial profile
FPG=fasting plasma glucose. ITT=intention-to-treat.

criteria (appendix). The study did not have a dedicated data safety monitoring board because the drugs have known safety profiles.

Statistical analysis

We calculated the sample size from previous studies of dapagliflozin or once-weekly exenatide, estimating an HbA_{1c} reduction of 0·35% (3·8 mmol/mol) for exenatide plus dapagliflozin versus either drug alone. To detect this difference with an SD of 1·1% (12·0 mmol/mol), 209 participants per group were required for 90% power at a two-sided significance level of 0·05. Under the assumption of a 5% dropout rate before first HbA_{1c} assessment, 220 patients per treatment group were required. An assumed screen failure of 40% would require investigators to screen 1100 participants.

We analysed primary and secondary efficacy variables in the intention-to-treat population, defined as all randomly assigned patients who received at least one dose of study drug with at least one post-baseline HbA_{1c} assessment. As a supportive analysis, we analysed the primary efficacy endpoint in the per-protocol analysis set, defined as a subset of the intention-to-treat population with exclusion of participants with one or more important protocol violations (inadequate compliance, use of restricted medications during the trial conduct, study medication dosing error, deviations from the key inclusion and exclusion criteria, clinically important abnormalities noted before the first day of assigned study treatment, and previous exposure to exenatide treatment). We analysed safety data in the safety analysis set, defined as all randomly assigned patients who received at least one dose of study drug. The primary endpoint was assessed with a mixed-effects model for repeated measures (MMRM), with change in HbA_{1c} as the dependent variable; treatment, region, baseline HbA_{1c} stratum (<9·0% *vs* ≥9·0% [<75 *vs* ≥75 mmol/mol]), week, and treatment-by-week interaction as fixed factors; and baseline HbA_{1c} as a continuous covariate. An unstructured covariance structure was used to model within-patient errors. We used the Kenward–Roger approximation to estimate denominator degrees of freedom. Changes in other continuous endpoints were tested with MMRM analyses or an analysis-of-covariance model. We analysed categorical variables with a Cochran–Mantel–Haenszel test stratified by baseline HbA_{1c} stratum; patients with missing data at week 28 were assumed to be non-responders. Safety data were summarised descriptively, with all adverse events coded with MedDRA version 18.1.

Hypothesis testing for the primary and secondary efficacy endpoints followed a serial gated procedure to control for family-wise type I error. Superiority of exenatide plus dapagliflozin versus both exenatide and dapagliflozin alone was required at a two-sided significance level of p<0·05 for stepwise sequential testing to proceed. The testing sequence had eight steps: (1) change in HbA_{1c} from baseline to week 28 (primary endpoint), (2) change in weight from baseline to week 28, (3) change in FPG from baseline to week 28, (4) change in 2 h postprandial glucose from baseline to week 28, (5) proportion of patients with at least 5·0% weight loss at week 28, (6) change in FPG from baseline to week 2, (7) proportion of patients achieving an HbA_{1c} of less than 7·0% (<53 mmol/mol) at week 28, and (8) change in systolic blood pressure from baseline to week 28. Nominal p values were calculated for exploratory endpoints and subgroup analyses.

We did statistical analyses with SAS (versions 9.2 and 9.4). This trial is registered with ClinicalTrials.gov, number NCT02229396.

	Exenatide plus dapagliflozin group (n=228)	Exenatide group (n=227)	Dapagliflozin group (n=230)
Age (years)	54 (10)	54 (10)	55 (9)
≥65	31 (14%)	28 (12%)	26 (11%)
Sex			
Female	126 (55%)	111 (49%)	120 (52%)
Male	102 (45%)	116 (51%)	110 (48%)
Race			
White	190 (83%)	194 (85%)	189 (82%)
Black	34 (15%)	27 (12%)	33 (14%)
Asian	3 (1%)	1 (<1%)	1 (<1%)
Other	1 (<1%)	5 (2%)	7 (3%)
Hispanic ethnic origin	95 (42%)	91 (40%)	85 (37%)
Weight (kg)	91·8 (22·2)	89·8 (20·2)	91·1 (19·7)
BMI (kg/m²)	33·2 (6·8)	32·0 (5·9)	33·0 (6·1)
BMI group			
<25 kg/m²	17 (7%)	17 (7%)	15 (6%)
≥25 to <30 kg/m²	71 (31%)	78 (34%)	57 (25%)
≥30 kg/m²	140 (61%)	132 (58%)	158 (69%)
HbA_{1c} (%)	9·3 (1·1)	9·3 (1·1)	9·3 (1·0)
HbA_{1c} group			
<8%	14 (6%)	13 (6%)	14 (6%)
≥8% to <9%	84 (37%)	84 (37%)	88 (38%)
≥9%	130 (57%)	130 (57%)	128 (56%)
Duration of type 2 diabetes (years)	7·6 (6·0)	7·4 (5·5)	7·1 (5·5)
FPG (mmol/L)	11·0 (2·6)	10·8 (2·4)	10·9 (2·3)
Systolic blood pressure (mm Hg)	130·5 (12·2)	129·6 (12·6)	129·7 (13·0)
Diastolic blood pressure (mm Hg)	78·7 (7·7)	78·4 (8·0)	78·0 (8·1)
eGFR (mL/min per 1·73 m²)*	97·7 (23·7)	99·4 (26·8)	97·5 (24·0)
eGFR group			
≥30 to <60 mL/min per 1·73 m²	6 (3%)	7 (3%)	12 (5%)
≥60 mL/min per 1·73 m²	222 (97%)	220 (97%)	218 (95%)

Data are mean (SD) or n (%). To convert HbA_{1c} from a percentage to mmol/mol, multiply by 10·93 and subtract 23·50. To convert FPG from mmol/L to mg/dL, divide by 0·0555. FPG=fasting plasma glucose. eGFR=estimated glomerular filtration rate. *Calculated with the Modification of Diet in Renal Disease calculator.

Table 1: Demographic and baseline characteristics

Role of the funding source

The funder of the study was involved in the study design and protocol development, provided logistical support,

and obtained the data, which were evaluated jointly with the authors. All authors interpreted the data and wrote the report with the support of the funder's medical writing services. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Sept 4, 2014, and Oct 15, 2015, we randomly assigned 695 patients to receive exenatide plus dapagliflozin (n=231), exenatide alone (n=231; n=1 untreated), or dapagliflozin alone (n=233). 685 participants comprised the intention-to-treat population, of whom 611 (88%)

	Exenatide plus dapagliflozin group (n=228)	Exenatide group (n=227)	Dapagliflozin group (n=230)	Between-group difference	
				Exenatide plus dapagliflozin *vs* exenatide	Exenatide plus dapagliflozin *vs* dapagliflozin
HbA_{1c} (%), intention-to-treat analysis					
n	197	192	198	..	..
Baseline	9·3 (1·1)	9·3 (1·1)	9·3 (1·0)	..	..
Week 28	7·3 (1·3)	7·6 (1·3)	7·8 (1·1)	..	..
Change	−2·0 (−2·1 to −1·8)	−1·6 (−1·8 to −1·4)	−1·4 (−1·6 to −1·2)	−0·4 (−0·6 to −0·1); p=0·004	−0·6 (−0·8 to −0·3); p<0·001
Prespecified subgroup analysis*					
Baseline HbA_{1c} <8%†					
n	11	13	14	..	..
Baseline	7·6 (0·4)	7·6 (0·4)	7·7 (0·3)	..	..
Week 28	6·4 (0·6)	7·2 (1·2)	7·0 (0·7)	..	..
Change	−1·6 (−2·3 to −0·9)	−0·7 (−1·4 to −0·0)	−1·0 (−1·7 to −0·4)	−0·9 (−1·9 to 0·1); p=0·089	−1·0 (−1·5 to 0·4); p=0·263
Baseline HbA_{1c} ≥8% to <9%					
n	75	75	76	..	..
Baseline	8·5 (0·3)	8·5 (0·3)	8·5 (0·3)	..	..
Week 28	7·0 (1·1)	7·4 (1·1)	7·6 (1·0)	..	..
Change	−1·7 (−2·0 to −1·4)	−1·3 (−1·6 to −1·0)	−1·0 (−1·3 to −0·7)	−0·4 (−0·8 to −0·0); p=0·047	−0·7 (−1·1 to −0·3); p<0·001
Baseline HbA_{1c} ≥9%					
n	111	104	108	..	..
Baseline	10·1 (0·8)	10·0 (0·8)	10·0 (0·7)	..	..
Week 28	7·6 (1·4)	7·8 (1·5)	7·9 (1·2)	..	..
Change	−2·2 (−2·4 to −1·9)	−1·9 (−2·1 to −1·6)	−1·6 (−1·9 to −1·4)	−0·3 (−0·6 to 0·0); p=0·085	−0·5 (−0·8 to −0·2); p=0·002
HbA_{1c} (%), per-protocol analysis*					
n	185	180	184	..	..
Baseline	9·3 (1·1)	9·2 (1·0)	9·3 (1·0)	..	..
Week 28	7·3 (1·3)	7·7 (1·3)	7·8 (1·2)	..	..
Change	−2·0 (−2·2 to −1·8)	−1·5 (−1·7 to −1·3)	−1·4 (−1·5 to −1·2)	−0·5 (−0·8 to −0·2); p<0·001	−0·7 (−0·9 to −0·4); p<0·001
HbA_{1c} <7·0% at week 28	102 (45%)	62 (27%)	44 (19%)	17%; p<0·001	26%; p<0·001
HbA_{1c} ≤6·5% at week 28	69 (30%)	43 (19%)	24 (10%)	11%; p=0·005	20%; p<0·001
FPG (mmol/L)					
n	223	219	225	..	..
Baseline	11·06 (3·02)	10·67 (2·82)	10·57 (2·63)	..	..
Week 2	8·75 (2·26)	9·73 (2·72)	9·36 (2·40)	..	..
Change	−2·30 (−2·59 to −2·02)	−1·19 (−1·48 to −0·90)	−1·46 (−1·75 to −1·18)	−1·12 (−1·50 to −0·74); p<0·001	−0·84 (−1·22 to −0·46); p<0·001
n	198	190	198	..	..
Baseline	10·86 (2·95)	10·49 (2·76)	10·49 (2·45)	..	..
Week 28	7·23 (1·93)	8·25 (2·79)	7·94 (2·01)	..	..
Change	−3·61 (−3·93 to −3·29)	−2·50 (−2·83 to −2·17)	−2·70 (−3·02 to −2·37)	−1·11 (−1·55 to −0·67); p<0·001	−0·91 (−1·35 to −0·48); p<0·001
2 h PPG (mmol/L)					
n	200	191	199	..	..
Baseline	14·94 (3·74)	14·77 (3·72)	14·53 (3·34)	..	..
Week 28	9·92 (2·75)	11·42 (3·42)	11·23 (3·02)	..	..
Change	−4·83 (−5·28 to −4·39)	−3·31 (−3·78 to −2·84)	−3·41 (−3·86 to −2·96)	−1·52 (−2·09 to −0·96); p<0·001	−1·42 (−1·99 to −0·86); p<0·001

(Table 2 continues on next page)

	Exenatide plus dapagliflozin group (n=228)	Exenatide group (n=227)	Dapagliflozin group (n=230)	Between-group difference	
				Exenatide plus dapagliflozin *vs* exenatide	Exenatide plus dapagliflozin *vs* dapagliflozin
(Continued from previous page)					
2 h PPG increment (mmol/L)*‡					
n	209	201	208	..	..
Baseline	4·01 (2·74)	4·15 (2·70)	4·00 (2·31)	..	..
Week 28	2·63 (2·19)	3·09 (2·34)	3·23 (2·20)	..	..
Change	−1·18 (−1·50, −0·86)	−0·75 (−1·08, −0·41)	−0·60 (−0·92, −0·28)	−0·43 (−0·84 to −0·03); p=0·036	−0·58 (−0·98 to −0·18); p=0·005
Weight (kg)					
n	198	192	198	..	..
Baseline	91·94 (21·77)	89·61 (18·81)	91·71 (19·55)	..	..
Week 28	88·29 (20·48)	88·15 (18·28)	88·49 (18·86)	..	..
Change	−3·41 (−3·97 to −2·85)	−1·54 (−2·11 to −0·98)	−2·19 (−2·75 to −1·64)	−1·87 (−2·66 to −1·08); p<0·001	−1·22 (−2·00 to −0·44); p=0·002
Prespecified subgroup analysis*					
Baseline HbA_{1c} <8%†					
n	11	13	14	..	..
Baseline	92·54 (17·48)	88·84 (19·87)	92·40 (20·14)	..	..
Week 28	88·33 (14·57)	87·00 (17·33)	89·01 (19·05)	..	..
Change	−3·97 (−6·33 to −1·61)	−2·13 (−4·37 to −0·11)	−3·64 (−5·80 to −1·48)	−1·84 (−5·09 to 1·40); p=0·266	−0·33 (−3·52 to 2·85); p=0·837
Baseline HbA_{1c} ≥8% to <9%					
n	75	75	76	..	..
Baseline	94·93 (22·77)	91·80 (16·47)	92·81 (19·48)	..	..
Week 28	90·50 (22·20)	90·26 (16·74)	90·67 (18·37)	..	..
Change	−4·47 (−5·39 to −3·55)	−1·93 (−2·85 to −1·02)	−2·18 (−3·08 to −1·28)	−2·54 (−3·82 to −1·25); p<0·001	−2·29 (−3·57 to −1·02); p<0·001
Baseline HbA_{1c} ≥9%					
n	112	104	108	..	..
Baseline	89·87 (21·39)	88·13 (20·24)	89·01 (19·55)	..	..
Week 28	86·80 (19·77)	86·78 (19·44)	86·88 (19·19)	..	..
Change	−2·59 (−3·35 to −1·83)	−1·17 (−1·94 to −0·40)	−1·97 (−2·72 to −1·21)	−1·42 (−2·47 to −0·37); p=0·008	−0·62 (−1·67 to 0·42); p=0·240
Weight loss ≥5%	76 (33%)	31 (14%)	46 (20%)	20%; p<0·001	13%; p=0·001
Systolic blood pressure (mm Hg)					
n	205	199	209	..	..
Baseline	130·5 (12·2)	129·6 (12·6)	129·7 (13·0)	..	..
Week 28	126·5 (13·2)	129·3 (12·5)	128·6 (13·8)	..	..
Change	−4·2 (−5·8 to −2·6)	−1·3 (−2·9 to 0·3)	−1·8 (−3·4 to −0·2)	−2·9 (−5·0 to −0·8); p=0·007	−2·4 (−4·5 to −0·3); p=0·025

Data are mean (SD), least-squares mean (95% CI), or n (%), unless otherwise specified. Observed values are given for HbA_{1c} at a given timepoint; change values were calculated with data modelling techniques. To convert HbA_{1c} from a percentage to mmol/mol, multiply by 10·93 and subtract 23·50. To convert FPG or 2 h PPG from mmol/L to mg/dL, divide by 0·0555. FPG=fasting plasma glucose. PPG=postprandial glucose. *p values for these supportive analyses are nominal. †Patients had an HbA_{1c} of 8–12% at screening, but in some individuals HbA_{1c} decreased to <8·0% between screening and baseline measurements. ‡The 2 h PPG increment from each standardised meal tolerance test was calculated as the 2 h PPG concentration minus the preprandial concentration.

Table 2: Primary, secondary, and associated efficacy endpoints

completed the study (figure 1). Treatment compliance was high (appendix). Demographic and baseline characteristics were similar across treatment groups, with the exception of fewer women in the exenatide group and fewer Hispanic patients in the dapagliflozin group (table 1).

Exenatide plus dapagliflozin significantly reduced HbA_{1c} from baseline to week 28 compared with exenatide or dapagliflozin and was significantly superior to either drug alone for all secondary efficacy endpoints (table 2). The prespecified per-protocol analysis showed findings consistent with the primary intention-to-treat analysis (table 2). A between-group difference in change in HbA_{1c} was apparent from the first assessment at week 4 (figure 2A). Significantly more patients achieved an HbA_{1c} of less than 7·0% (<53 mmol/mol) with exenatide plus dapagliflozin than with exenatide or dapagliflozin (figure 2B).

Patients receiving exenatide plus dapagliflozin had significantly greater FPG reductions from baseline than did those receiving either drug alone; reductions were apparent from week 2 (figure 2C). 2 h postprandial glucose concentrations and increments (2 h postprandial

concentration minus preprandial concentration) derived from the standardised meal tolerance test were likewise significantly reduced with exenatide plus dapagliflozin compared with exenatide or dapagliflozin alone (table 2; figure 2D). Daily average six-point SMBG concentration decreased from baseline to week 28 in all treatment groups (figure 2E; appendix), with the greatest reductions shown in patients receiving the combination therapy. Urinary glucose-to-creatinine ratio increased with both exenatide plus dapagliflozin and dapagliflozin alone, but this increase was consistently slightly less with the combination than with dapagliflozin alone (appendix).

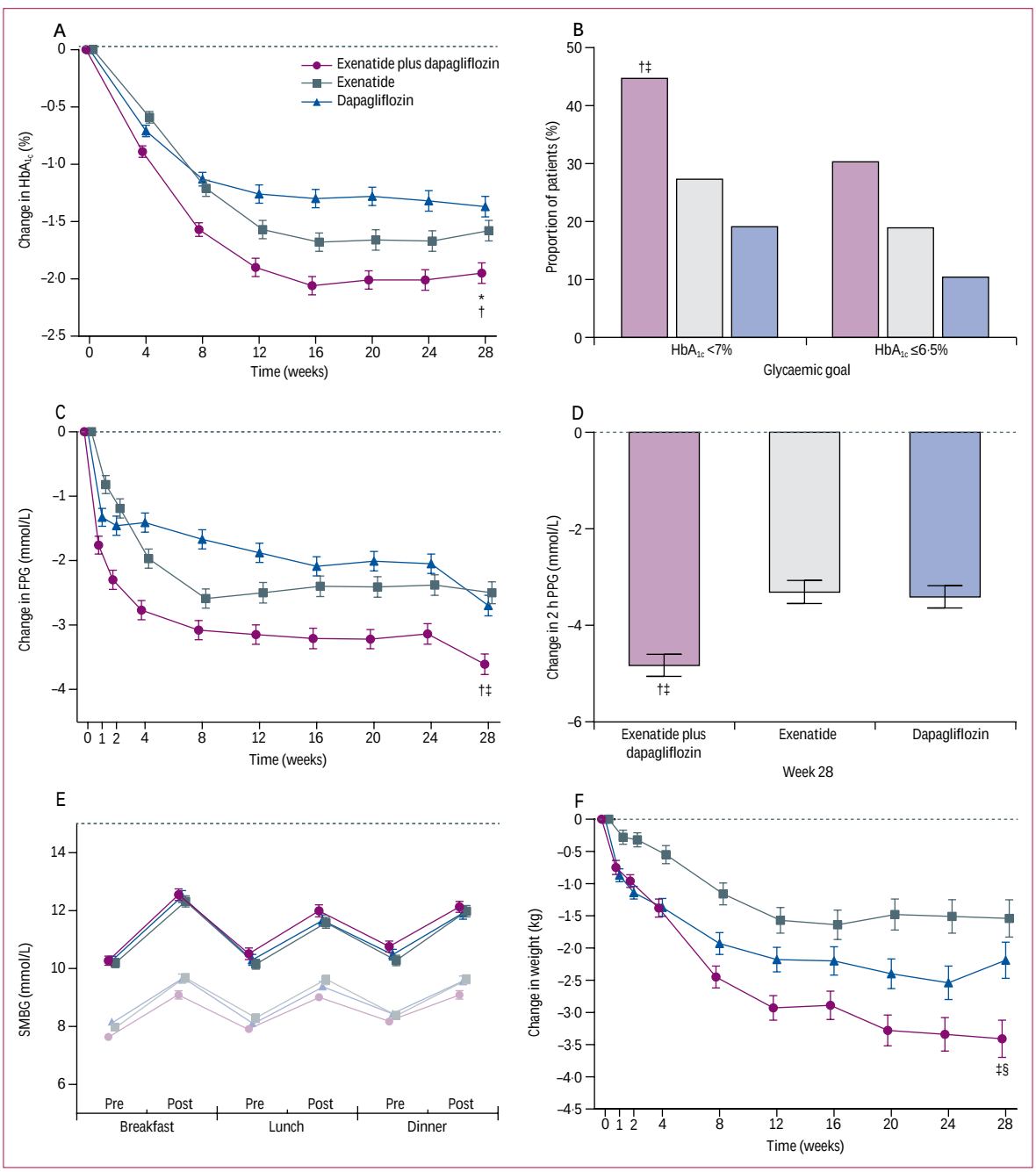

Figure 2: Primary, secondary, and exploratory endpoints in the intention-to-treat population
(A) Least-squares mean change in HbA_{1c}. (B) Proportion of patients achieving an HbA_{1c} target of less than 7% or of 6·5% or less at week 28. (C) Least-squares mean change in FPG. (D) Least-squares mean change in 2 h PPG. (E) Mean six-point SMBG profiles at baseline (closed symbols, solid lines) and week 28 (open symbols, dashed lines). (F) Least-squares mean change in weight. Error bars show SEs. To convert HbA_{1c} from a percentage to mmol/mol, multiply by 10·93 and subtract 23·50. To convert FPG, 2 h PPG, or SMBG from mmol/L to mg/dL, divide by 0·0555. FPG=fasting plasma glucose. PPG=postprandial glucose. SMBG=self-monitored blood glucose. *p<0·01 versus exenatide. †p<0·001 versus dapagliflozin. ‡p<0·001 versus exenatide. §p<0·01 versus dapagliflozin.

The proportion of patients initiating rescue therapy was higher in the dapagliflozin group than in the exenatide plus dapagliflozin or exenatide groups (7% [n=17] *vs* 4% [n=9] or 4% [n=10], respectively).

Exenatide plus dapagliflozin was associated with significantly greater reductions in weight from baseline to week 28 compared with exenatide or dapagliflozin alone (table 2). Weight loss continued up to week 28 in patients given exenatide plus dapagliflozin, but stabilised in those given exenatide or dapagliflozin alone (figure 2F). Changes in weight from baseline were greatest in patients with baseline HbA_{1c} values of 8% or more to less than 9% (≥64 to <75 mmol/mol; table 2). Weight loss of 5% or greater was achieved more often with exenatide plus dapagliflozin than with the individual drugs (table 2).

Exenatide plus dapagliflozin treatment was associated with a significantly greater reduction in systolic blood pressure from baseline to week 28 than was either drug alone (table 2). No intergroup differences were noted for diastolic blood pressure or lipid measures, although we recorded a numerical improvement in triglycerides in all treatment groups (appendix). Treatment satisfaction and weight-related quality of life mostly stayed the same or improved in each group; neither outcome differed significantly between groups (appendix).

Exenatide plus dapagliflozin was well tolerated, with similar overall rates of adverse and serious adverse events between groups in the safety analysis set (table 3). Five (1%) of 694 patients died: three patients in the exenatide plus dapagliflozin group (coronary artery arteriosclerosis, multiple injuries [homicide], and oxycodone–doxylamine intoxication) and one patient each in the exenatide group (myocardial infarction) and the dapagliflozin group (ischaemic stroke; table 3). No death was deemed related to study drugs. Potential cardiovascular events and hepatic events were adjudicated (table 3). No episodes of major or minor hypoglycaemia were reported. Episodes of hypoglycaemia associated with blood glucose values of 3·0 mmol/L or greater were reported by less than 4% of patients during the study period and were more common with combination therapy (table 3); events were mild or moderate, with SMBG ranging between 3·0 mmol/L and 4·2 mmol/L during episodes. The most common adverse events (≥5% of patients in any group) were diarrhoea, injection-site nodules, nausea, and urinary tract infections (table 3). Gastrointestinal and injection-site-related adverse events were more common in patients in the exenatide plus dapagliflozin and exenatide groups than in those in the dapagliflozin group (table 3).

Incidences of potentially volume depletion-related adverse events, marked abnormalities of haematocrit, and acute renal disorders were low and similar between groups (table 3). Although a small difference in eGFR at week 28 was evident between the dapagliflozin and the exenatide plus dapagliflozin groups, the trajectory of change—an initial drop followed by steady recovery—was

	Exenatide plus dapagliflozin group (n=231)	Exenatide group (n=230)	Dapagliflozin group (n=233)
Any adverse event	131 (57%)	124 (54%)	121 (52%)
Any serious adverse event	10 (4%)	8 (3%)	10 (4%)
Deaths	3 (1%)	1 (<1%)	1 (<1%)
Adverse events leading to discontinuation	9 (4%)	11 (5%)	5 (2%)
Adverse events occurring in ≥5% of patients			
Diarrhoea	10 (4%)	13 (6%)	7 (3%)
Injection-site nodule	18 (8%)	14 (6%)	12 (5%)
Nausea	12 (5%)	17 (7%)	7 (3%)
Urinary tract infection	10 (4%)	12 (5%)	13 (6%)
Adverse events of special interest			
Volume depletion-related events	2 (1%)	0	3 (1%)
Dehydration	2 (1%)	0	0
Hypotension	0	0	2 (1%)
Syncope	0	0	1 (<1%)
Haematocrit >55%	2 (1%)	0	4 (2%)
Pancreatitis	1 (<1%)	1 (<1%)	0
Acute renal disorders	0	2 (1%)	1 (<1%)
Acute kidney injury	0	1 (<1%)	0
Renal failure	0	1 (<1%)	1 (<1%)
Events suggestive of genital infections	10 (4%)	4 (2%)	13 (6%)
Gastrointestinal events	36 (16%)	35 (15%)	27 (12%)
Injection-site-related events	28 (12%)	27 (12%)	16 (7%)
Nodule	18 (8%)	14 (6%)	12 (5%)
Induration	4 (2%)	6 (3%)	2 (1%)
Bruising	4 (2%)	4 (2%)	2 (1%)
Pruritus	2 (1%)	2 (1%)	2 (1%)
Injection-site mass	0	2 (1%)	2 (1%)
Injection-site reaction	3 (1%)	0	0
Erythema	0	2 (1%)	1 (<1%)
Inflammation	2 (1%)	0	0
Dermatitis	0	0	1 (<1%)
Hypersensitivity	0	1 (<1%)	0
Adjudicated cardiovascular events	3 (1%)	2 (1%)	2 (1%)
Adjudicated hepatic events	0	1 (<1%)	1 (<1%)
Hypoglycaemia			
Major	0	0	0
Minor	0	0	0
Other	8 (3%)	3 (1%)	3 (1%)
Mild	7 (3%)	3 (1%)	2 (1%)
Moderate	1 (<1%)	0	2 (1%)
Severe	0	0	0
Highest anti-exenatide antibody concentrations over study period			
Negative	58 (26%)	54 (24%)	..
High positive (≥625)	95 (42%)	64 (28%)	..
Low positive (<625)	74 (33%)	108 (48%)	..
Any positive	169 (74%)	172 (76%)	..

Data are n (%).

Table 3: Adverse events (safety analysis set)

similar in these groups (appendix). The incidence of urinary tract infections was balanced between groups; however, more patients in the exenatide plus dapagliflozin and dapagliflozin treatment groups had an event suggestive of genital infection (table 3). Pancreatitis was reported in two (<1%) patients (n=1 each in the exenatide plus dapagliflozin and exenatide groups). One (<1%) patient in the exenatide group, but none in the other groups, had diabetic ketoacidosis. No pancreatic, thyroid, or bladder neoplasms were reported.

Vital signs and laboratory tests were examined for safety signals. Consistent small mean changes from baseline were recorded over time in heart rate (exenatide-treated groups) or urinary glucose-to-creatinine ratio, haematocrit, haemoglobin, and uric acid (dapagliflozin-treated groups), but there was no separation between the SDs of these variables between groups (appendix).

Over 28 weeks, 169 (74%) patients in the exenatide plus dapagliflozin group and 172 (76%) patients in the exenatide group developed anti-exenatide antibodies (table 3), with no detected effect on glycaemic control (appendix). The number of patients testing positive for anti-exenatide antibodies peaked at week 12 and decreased thereafter (data not shown). Patients who were antibody positive reported more injection-site-related adverse events (nodules, induration, bruising, and pruritus) than did those who were antibody negative (appendix).

Discussion

In metformin-treated patients with inadequate HbA_{1c} control, concomitant use of the GLP-1 receptor agonist exenatide and the SGLT2 inhibitor dapagliflozin resulted in clinical improvements in glycaemic control, weight, and systolic blood pressure compared with use of either drug alone. These improvements occurred with no episodes of protocol-defined major or minor hypoglycaemia, and with no unexpected safety findings.

Scientific literature on the combination of a GLP-1 receptor agonist and an SGLT2 inhibitor is scarce. To the best of our knowledge, this is the first large-scale randomised controlled trial to test the efficacy and safety of this combination in patients with diabetes. Fulcher and colleagues[20] reported a small post-hoc subgroup analysis of the CANVAS study (NCT01032629), in which the SGLT2 inhibitor canagliflozin was added on to concomitant GLP-1 receptor agonist therapy, which showed reductions in HbA_{1c}, weight, and blood pressure. In a phase 2 study[21] in which once-weekly exenatide was combined with dapagliflozin in obese patients, significant weight loss, blood pressure reduction, and a reduction in the proportion of patients with prediabetes were reported, with no unexpected adverse events. Findings from real-world observational and retrospective analyses[22–24] suggest that these drug classes are already used together off-label in clinical practice.

In the present study, changes in efficacy endpoints could differ quantitatively between groups for different endpoints (eg, less than additive, additive, or synergistic). We speculated that glycaemic endpoints were likely to be less than additive because the efficacy of glucose-lowering therapies depends on baseline glycaemic control,[25] and the reduction of HbA_{1c} by one drug would reduce the HbA_{1c} change by the other;[15,16] however, these therapies were not likely to negate each other. Consistent with this theory, reductions in HbA_{1c}, FPG, and 2 h postprandial glucose were greater in patients given exenatide plus dapagliflozin than in those given either drug alone, but were not equal to the change reported for the individual drugs added together. Reductions in weight, systolic blood pressure, and triglycerides seemed to be additive, suggesting independent mechanisms resulting in changes that did not trigger compensatory counteracting responses. The additive effect on systolic blood pressure might have clinical significance, and can probably be explained by different mechanisms of blood pressure lowering. SGLT2 inhibitors have osmotic diuretic and natriuretic effects, which are associated with a small reduction in blood pressure,[15,26] whereas multiple pathways have been suggested for the effect of GLP-1 receptor agonists, including vasodilation and natriuresis.[26]

How weight loss would be affected by co-administration of exenatide and dapagliflozin was uncertain because complex compensatory mechanisms were anticipated: weight loss with an SGLT2 inhibitor is consistently less than calculated from glucose loss, presumably because of increased food intake,[21] whereas GLP-1 receptor agonists suppress appetite.[6] No single mechanism balancing bodyweight and energy expenditure has been identified, so the effects of drug interventions on this system are unpredictable. Our results showed that weight loss with the dual add-on treatment was additive, with roughly double the weight lost by patients receiving exenatide plus dapagliflozin compared with those receiving exenatide or dapagliflozin alone. This finding suggests that the complementary actions of GLP-1 receptor agonists, to reduce appetite and calorie intake, and SGLT2 inhibitors, to cause calorie loss through glycosuria, reset the system to some extent and are not completely compensated for. Weight loss was most pronounced in the subgroup of patients with a baseline HbA_{1c} value of 8–9% (64–75 mmol/mol) compared with those with a baseline value greater than 9% (>75 mmol/mol), potentially because patients with a higher HbA_{1c} were catabolic at baseline and weight loss was blunted by improved glycaemic control, with improvement in catabolic state. This effect might be explained by the additional mechanisms of glucose lowering by exenatide, such as increased insulin secretion, which result in increased glucose uptake by the tissues instead of loss via urinary excretion. Furthermore, the possibility of pre-existing dehydration in patients with more severe hyperglycaemia could be reversed by improved glycaemic control, leading to numerically less weight reduction.

Reductions in HbA_{1c} were significantly greater in the exenatide plus dapagliflozin group than in the groups given exenatide or dapagliflozin alone from week 4 to week 28, and HbA_{1c} seemed to stabilise at different timepoints (at weeks 16, 12, and 8, respectively). The difference between the combination and individual therapies for FPG was likewise apparent early, with a significantly greater decrease with exenatide plus dapagliflozin than with exenatide or dapagliflozin alone from as early as week 1. Small increases in cholesterol measures with dapagliflozin[15] were mitigated with the combination.

Whether the effects of adding a GLP-1 receptor agonist and an SGLT2 inhibitor sequentially would provide the same results as simultaneous addition is unclear. If both agents were initiated sequentially within 28 weeks, the HbA_{1c} change after both treatments had achieved their full effect is likely to be similar to the result of dual addition after 28 weeks, assuming a similar patient population. However, due to the well documented treatment inertia in clinical practice, the patients would be at risk of having protracted periods of inadequate glycaemic control with sequential add-on treatment. Hypothetically, longer periods of poor glycaemic control might result in more rapid disease progression and less than equivalent glycaemic control compared with adding the drugs within 28 weeks.

Cardiovascular outcome studies of a long-acting GLP-1 receptor agonist (liraglutide; LEADER; NCT01179048)[9] and an SGLT2 inhibitor (empagliflozin; EMPA-REG OUTCOME; NCT01131676)[10] have both shown reductions in the composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. Although the ELIXA study[27] of the short-acting GLP-1 receptor agonist lixisenatide showed no significant reduction in the primary composite endpoint of cardiovascular death, myocardial infarction, stroke, or hospital admission for unstable angina, the cardiovascular effects of lixisenatide might differ from those of long-acting GLP-1 receptor agonists. Cardiovascular outcome trials of exenatide (EXSCEL; NCT01144338) and dapagliflozin (DECLARE TIMI-58: NCT01730534) are ongoing and will help to establish whether these cardiovascular benefits are class effects. Our findings show that, compared with treatment with exenatide or dapagliflozin alone, treatment with the drugs combined resulted in more pronounced improvements in HbA_{1c}, weight, and systolic blood pressure—all of which are important cardiovascular risk factors. Hypoglycaemia is also an important consideration for patients at high cardiovascular risk. Although aspects of the design of the present study, such as the high HbA_{1c} inclusion criteria, could have been influential, that the risk of hypoglycaemia was low with the combination therapy is encouraging. However, the possibility that the combination of a GLP-1 receptor agonist and an SGLT2 inhibitor might provide additional cardiovascular benefit compared with either class alone requires further assessment.

Treatment with exenatide plus dapagliflozin added to metformin might have advantages over other combinations for patients with poor HbA_{1c} control. Compared with DPP-4 inhibitors, greater reductions in HbA_{1c}, weight, and blood pressure have generally been reported with GLP-1 receptor agonists.[28,29] The combination of a GLP-1 receptor agonist with insulin is more likely to evoke hypoglycaemia in at-risk patients, with few blood pressure and weight effects.[30]

Renal effects of the GLP-1 receptor agonist and SGLT2 inhibitor combination are of interest. The initial drop in eGFR followed by stabilisation to baseline levels observed in both dapagliflozin-treated groups in our study, and commonly reported in other dapagliflozin clinical trials, is not thought to represent a pathological renal change. Rather, these changes might confer renoprotection via reduced glomerular hyperfiltration and restoration of tubuloglomerular feedback.[31] Findings from the EMPA-REG OUTCOME study[7] show a reduction in the progression of renal disease and the rate of renal adverse events in patients with type 2 diabetes treated with empagliflozin, including those with impaired renal function at baseline. Further studies are needed to determine whether these findings are a class effect of SGLT2 inhibitors.

Limitations of our study include the fairly short duration (28 weeks), although a long-term extension of the trial will provide up to 2 years of controlled data. We excluded patients with baseline HbA_{1c} values less than 8% (<64 mmol/mol) and patients with an eGFR less than 60 mL/min per 1·73 m², so the results cannot be generalised to these populations. Moreover, the study did not have a placebo-only group, which would have allowed the contributions of drugs versus placebo to be defined, including the potential non-specific effect associated with clinical trial participation, and would have allowed for a clearer assessment of adverse events directly attributable to the study medications. The low frequency of hypoglycaemia could be due to several factors, including the intrinsic glucose-dependent properties of both drug classes studied. The HbA_{1c} inclusion criterion of 8–12% (64–108 mmol/mol) led to high baseline HbA_{1c} (9·3% [78 mmol/mol]) and FPG (10·9 mmol/L), which reduced the likelihood of glucose falling below the predefined concentration of less than 3·0 mmol/L. The definition of hypoglycaemia was consistent with that used in previous studies and based on the 2010 European Medicines Agency diabetes guidance,[32] but was more stringent than the definition proposed by the American Diabetes Association and the European Association for the Study of Diabetes (<3·9 mmol/L).[33,34] Finally, we did not explore the effects (particularly on weight) of combining a GLP-1 receptor agonist and an SGLT2 inhibitor with concomitant intensive dietary or lifestyle intervention, or the benefits of sequential rather than simultaneous combination.

The present study provides high-quality evidence that the combination of exenatide and dapagliflozin is more

effective than either drug alone in patients with inadequate response to metformin monotherapy. Additional data from ongoing studies investigating the sequential addition of an SGLT2 inhibitor to a GLP-1 receptor agonist (eg, AWARD-10; NCT02597049) will provide further evidence about the use of these classes in combination. Cost analyses are needed to establish the cost-effectiveness of this combined treatment approach.

Contributors

JPF, CG, and EH contributed to study conduct and data interpretation, provided critical review, and edited and approved the report. AA contributed to study conduct, provided critical review, and approved the report. FD devised the statistical analysis plan, reviewed all data, interpreted data, provided critical review, and approved the report. PÖ contributed to study design and data interpretation, provided critical review, and approved the report. SAJ contributed to study design and conduct, interpreted data, provided critical review, and approved the report.

Declaration of interests

JPF has received research grants from AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, CeQur, Elcelyx, Eli Lilly, Intarcia, Ionis, Janssen, Johnson & Johnson, Merck, Novo Nordisk, Pfizer, Sanofi, Theracos, and vTv, and has served on scientific advisory boards and received consulting fees from AstraZeneca, CeQur, Johnson & Johnson, and Sanofi. CG has served on scientific advisory boards and received consulting fees from Alfa Wasserman, AstraZeneca, Bayer, Berlin Chemie Menarini, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck, MSD, Novartis, Novo Nordisk, Sanofi, Servier Pharma, and Worwag Pharma. EH is an employee and stockholder of AstraZeneca. AA has received research grants from AbbVie, AstraZeneca, Novo Nordisk, and Sanofi-Aventis. FD is an employee and stockholder of AstraZeneca. PÖ is an employee and stockholder of AstraZeneca. SAJ has received consulting fees from AstraZeneca, Eli Lilly, and Janssen.

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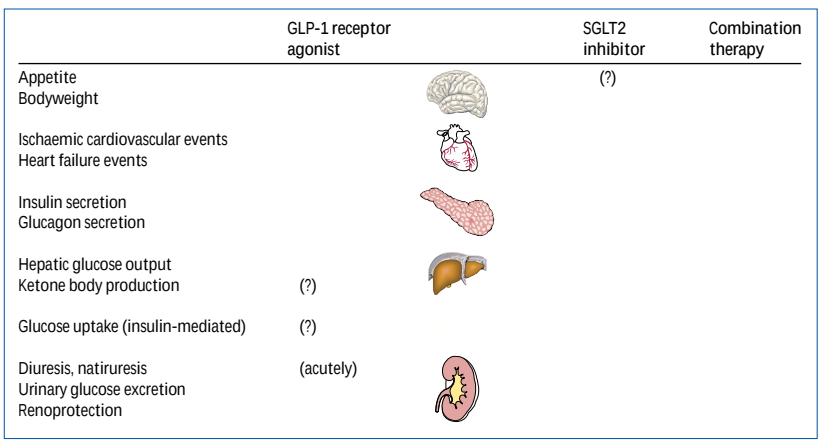

Figure: E ects of GLP-1 receptor agonists and SGLT2 inhibitors alone and in combination
Schematic diagram showing qualitative e ects at the level of the CNS, the heart, the endocrine pancreas (cells, insulin secretion; cells, glucagon secretion), the liver, and the kidney. Question marks signify some uncertainty about the signi cance of the e ect indicated by the neighbouring arrow. E ects of combination therapy are based on ndings from Frias and colleagues study[1] or on inference from mechanistic studies. GLP-1=glucagon-like peptide-1. SGLT2=sodium-glucose cotransporter-2.

In relationships between people, some couples will be happy, others less so. The success of their combination will depend on the interplay of factors contributed by each individual. Some of them will point in the same direction, thus reinforcing whatever one partner already contributed. For GLP-1 receptor agonists and SGLT2 inhibitors, this notion applies to control of glucose, reductions in bodyweight and systolic blood pressure, avoidance of hypoglycaemia, and perhaps the potential to enhance any cardiovascular bene t that either class might be able to provide (gure). However, even opposing e ects on some factors might be welcome, as checks and balances to prevent excessive e ects that might lead to potential damage, if unopposed. Such potential damage might arise as a result of the contrasting actions of GLP-1 receptor agonists[2] and SGLT2 inhibitors[3] on glucagon secretion and, consequentially, on formation of ketone bodies, and their potentially deleterious (ketoacidosis)[6] or bene cial (substrate supply)[7] actions (gure). GLP-1 receptor agonists, which tended to be coupled with insulin treatment in the past,[10] might want to rethink their partnership status and carefully check the potential for a preferred relationship with SGLT2 inhibitors.

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