Once-weekly dulaglutide versus bedtime insulin glargine, both in combination with prandial insulin lispro, in patients with type 2 diabetes (AWARD-4): a randomised, open-label, phase 3, non-inferiority study

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Summary

Background For patients with type 2 diabetes who do not achieve target glycaemic control with conventional insulin treatment, advancing to a basal–bolus insulin regimen is often recommended. We aimed to compare the efficacy and safety of long-acting glucagon-like peptide-1 receptor agonist dulaglutide with that of insulin glargine, both combined with prandial insulin lispro, in patients with type 2 diabetes.

Methods We did this 52 week, randomised, open-label, phase 3, non-inferiority trial at 105 study sites in 15 countries. Patients (aged ≥18 years) with type 2 diabetes inadequately controlled with conventional insulin treatment were randomly assigned (1:1:1), via a computer-generated randomisation sequence with an interactive voice-response system, to receive once-weekly dulaglutide 1·5 mg, dulaglutide 0·75 mg, or daily bedtime glargine. Randomisation was stratified by country and metformin use. Participants and study investigators were not masked to treatment allocation, but were unaware of dulaglutide dose assignment. The primary outcome was a change in glycated haemoglobin A_{1c} (HbA_{1c}) from baseline to week 26, with a 0·4% non-inferiority margin. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01191268.

Findings Between Dec 9, 2010, and Sept 21, 2012, we randomly assigned 884 patients to receive dulaglutide 1·5 mg (n=295), dulaglutide 0·75 mg (n=293), or glargine (n=296). At 26 weeks, the adjusted mean change in HbA_{1c} was greater in patients receiving dulaglutide 1·5 mg (–1·64% [95% CI –1·78 to –1·50], –17·93 mmol/mol [–19·44 to –16·42]) and dulaglutide 0·75 mg (–1·59% [–1·73 to –1·45], –17·38 mmol/mol [–18·89 to –15·87]) than in those receiving glargine (–1·41% [–1·55 to –1·27], –15·41 mmol/mol [–16·92 to –13·90]). The adjusted mean difference versus glargine was –0·22% (95% CI –0·38 to –0·07, –2·40 mmol/mol [–4·15 to –0·77]; p=0·005) for dulaglutide 1·5 mg and –0·17% (–0·33 to –0·02, –1·86 mmol/mol [–3·61 to –0·22]; p=0·015) for dulaglutide 0·75 mg. Five (<1%) patients died after randomisation because of septicaemia (n=1 in the dulaglutide 1·5 mg group); pneumonia (n=1 in the dulaglutide 0·75 mg group); cardiogenic shock; ventricular fibrillation; and an unknown cause (n=3 in the glargine group). We recorded serious adverse events in 27 (9%) patients in the dulaglutide 1·5 mg group, 44 (15%) patients in the dulaglutide 0·75 mg group, and 54 (18%) patients in the glargine group. The most frequent adverse events, arising more often with dulaglutide than glargine, were nausea, diarrhoea, and vomiting.

Interpretation Dulaglutide in combination with lispro resulted in a significantly greater improvement in glycaemic control than did glargine and represents a new treatment option for patients unable to achieve glycaemic targets with conventional insulin treatment.

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See **Comment** page 2020

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Introduction

Patients with type 2 diabetes who do not achieve or maintain desired glycaemic control with basal insulin, with or without oral drugs, often receive treatment intensification with the addition of multiple doses of prandial insulin (ie, a basal–bolus regimen).[1,2] However, studies[3–6] have shown that only 36–69% of these patients who receive basal–bolus treatment achieve optimum glycaemic control (glycated haemoglobin A_{1c} [HbA_{1c}] <7·0% [<53 mmol/mol]), but frequently have hypoglycaemia and weight gain.

Glucagon-like peptide-1 (GLP-1) receptor agonists enhance insulin secretion and suppress glucagon secretion in a glucose-dependent manner. They also enhance satiety and reduce appetite and food intake. More recently, these drugs have been investigated as a new treatment option for patients not achieving glycaemic control with basal insulin. Compared with the addition of prandial insulin lispro, addition of the once-weekly GLP-1 receptor agonist albiglutide or twice-daily exenatide to glargine resulted in similar glycaemic control with less hypoglycaemia and weight loss.[7,8] Similar improvement in glycaemic control achieved with a combination of basal insulin and GLP-1 receptor agonist versus basal–bolus treatment suggests other combinations, such as that of a GLP-1 receptor agonist with prandial insulin, should be explored for potential clinical benefit.

Dulaglutide is a long-acting GLP-1 receptor agonist in development as a once-weekly subcutaneous injection for patients with type 2 diabetes. Clinical trials have shown that treatment with dulaglutide is associated with improvements in glycaemic control, weight reduction, and low risk of hypoglycaemia.[9–13] We did the AWARD-4 trial to assess the efficacy and safety of prandial insulin combined with dulaglutide as an alternative to basal–bolus treatment in patients with late-stage type 2 diabetes inadequately controlled with conventional insulin treatment.

Methods

Study design and participants

We did this 52 week, randomised, open-label, phase 3, non-inferiority trial at 105 sites in 15 countries in Argentina, Australia, Belgium, Brazil, Canada, Denmark, Greece, Hungary, Mexico, Poland, Russia, Spain, Sweden, Taiwan, and the USA. Eligible patients were aged 18 years or older and receiving one or two stable daily insulin doses (any combination of basal, basal with prandial, or premixed insulin, with or without oral antihyperglycaemia drugs). Enrolment criteria included HbA_{1c} concentrations of 7·0% or more (≥53 mmol/mol) and 11·0% or less (≤97 mmol/mol), and a body-mass index (BMI) of 23–45 kg/m² (appendix).

See Online for appendix

The protocol was approved at each site by an institutional review board and was done in accordance with the principles of the Declaration of Helsinki.[14] All patients provided written informed consent.

Randomisation and masking

Patients were randomly assigned (1:1:1), via a computer-generated randomisation sequence with an interactive voice-response system, to receive once-weekly dulaglutide 1·5 mg, dulaglutide 0·75 mg, or daily bedtime glargine. Randomisation was stratified by country and metformin use. Participants and study investigators were not masked to treatment allocation, but were unaware of dulaglutide dose assignment.

Procedures

Patients entered a 9 week lead-in period on their present insulin regimen. Metformin was allowed; other oral antihyperglycaemia drugs were discontinued. Patients receiving metformin were to have used 1500 mg per day or more by week 2 of the lead-in period. The metformin dose then remained stable for at least 6 weeks before randomisation and during the treatment period.

Patients assigned to glargine started the drug at 50% of the pre-randomisation dose of total daily insulin; the remaining 50% was applied to the initial lispro dose for all groups. Insulin dose was adjusted once or twice weekly. The glargine algorithm had a treat-to-target strategy, based on the median of the previous three fasting serum glucose values (appendix).[15] All groups also used a lispro dosing algorithm (appendix).[16] In the case of severe, persistent hyperglycaemia, patients discontinued study drug and new treatment was started (appendix).[1,17] These patients were allowed to remain in the study.

Independent committees adjudicated investigator-reported pancreatitis, adverse events of serious or severe abdominal pain without known cause, confirmed increases in concentrations of pancreatic enzymes (≥3×upper limit of normal [ULN]), deaths, and prespecified non-fatal cardiovascular adverse events.

Outcomes

The primary efficacy outcome was change in HbA_{1c} from baseline to week 26. Secondary efficacy outcomes were the proportion of patients achieving HbA_{1c} of less than 7·0% (<53 mmol/mol) or of 6·5% or less (≤48 mmol/mol), change in fasting serum glucose (measured at a central laboratory), self-monitored plasma glucose, bodyweight, BMI, insulin doses, composite endpoints, and patient-reported outcomes. Composite endpoints assessed the proportion of patients achieving HbA_{1c} less than 7·0% without documented symptomatic hypoglycaemia and, separately, without nocturnal or severe hypoglycaemia, alone or in combination with no weight gain. Patient-reported outcomes included perceived health status, as measured by the EuroQoL-5 dimension questionnaire; ability to do physical activities of daily living; affect of weight on self-perception; and a self-reported questionnaire of low blood sugar. Safety outcomes were adverse events, hypoglycaemic episodes, laboratory measures, vital signs, electrocardiograph results, pancreatic events, and study drug and study discontinuations. We defined total hypoglycaemia as plasma glucose concentrations of 3·9 mmol/L or less (or less than 3·0 mmol/L), or symptoms or signs, or both, attributable to hypoglycaemia.[18] Severe hypoglycaemia was determined by the investigator and defined as an episode requiring the assistance of another person to administer treatment.[18]

Statistical analysis

Assuming a zero difference in HbA_{1c} reduction between dulaglutide 1·5 mg and glargine, a sample size of 837 randomised patients (279 per group) with 248 completers per group (744 total) at 26 weeks would provide 90% power to show non-inferiority (0·4% margin) of dulaglutide 1·5 mg to glargine, with an SD of 1·3%. Non-inferiority of dulaglutide versus glargine for the primary outcome of a reduction in HbA_{1c} at 26 weeks would be claimed if the 95% upper confidence bound for the difference (dulaglutide 1·5 mg minus glargine) was less than the non-inferiority margin. All analyses were done based on the intention-to-treat population. For the primary objective, we used an ANCOVA model with the last post-baseline HbA_{1c} observation carried forward method, with treatment, country, and metformin use as fixed effects and baseline HbA_{1c} as a covariate. We used the same model to assess non-inferiority and superiority

of dulaglutide doses versus glargine, with a gatekeeping strategy to control family-wise type 1 error rate (appendix).[19] Adjusted p values were computed with the direct-calculation algorithm.[19] We used a similar analysis and gatekeeping strategy at 52 weeks. As a sensitivity analysis, we used a mixed-effects model repeated-measures (MMRM) approach, which included factors of treatment, country, metformin use, baseline HbA_{1c}, visit, and visit-by-treatment interaction in the model.

We used the MMRM approach for analyses of other continuous measures. We used the χ^2 test for categorical measures. We analysed bodyweight with ANCOVA and MMRM. Efficacy, bodyweight, and hypoglycaemia data obtained after patients stopped study drug but remained in the study were censored. We analysed the proportion of patients achieving HbA_{1c} target (last observation carried forward) with a logistic regression model with factors of treatment, country, metformin use, and baseline HbA_{1c}. We analysed hypoglycaemia rate with a generalised linear model with negative binomial distribution. We used the two-sided significance level of 0·05 for secondary endpoints. Results for primary and secondary analyses were only noted as significant if this threshold was met. No inference was provided with respect to clinical significance for any between-group differences recorded in this trial because of a scarcity of generally accepted criteria for such judgment. This study is registered with ClinicalTrials.gov, NCT01191268.

Role of the funding source

The funders of the study had direct oversight or participation in every stage of the study, including pharmacovigilance, study design, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all the primary data in the study and shared final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. Between Dec 9, 2010, and Sept 21, 2012, we randomly assigned 884 patients to receive dulaglutide 1·5 mg (n=295), dulaglutide 0·75 mg (n=293), or glargine (n=296), of whom 682 (77%) patients completed treatment up to week 52 (figure 1). Baseline characteristics were similar between groups (table 1). Overall, 676 (76%) patients took metformin, with similar proportions between groups.

At 26 weeks, the adjusted mean change from baseline in HbA_{1c} was greater with dulaglutide 1·5 mg (–1·64% [95% CI –1·78 to –1·50], –17·93 mmol/mol [–19·44 to –16·42]) and dulaglutide 0·75 mg (–1·59% [–1·73 to –1·45], –17·38 mmol/mol [–18·89 to –15·87]) than with glargine (–1·41% [–1·55 to –1·27], –15·41 mmol/mol [–16·92 to –13·90]; figure 2). The adjusted mean difference versus glargine was –0·22% (95% CI –0·38 to –0·07, –2·40 mmol/ml [–4·15 to –0·77]; p=0·005) for dulaglutide 1·5 mg and –0·17%

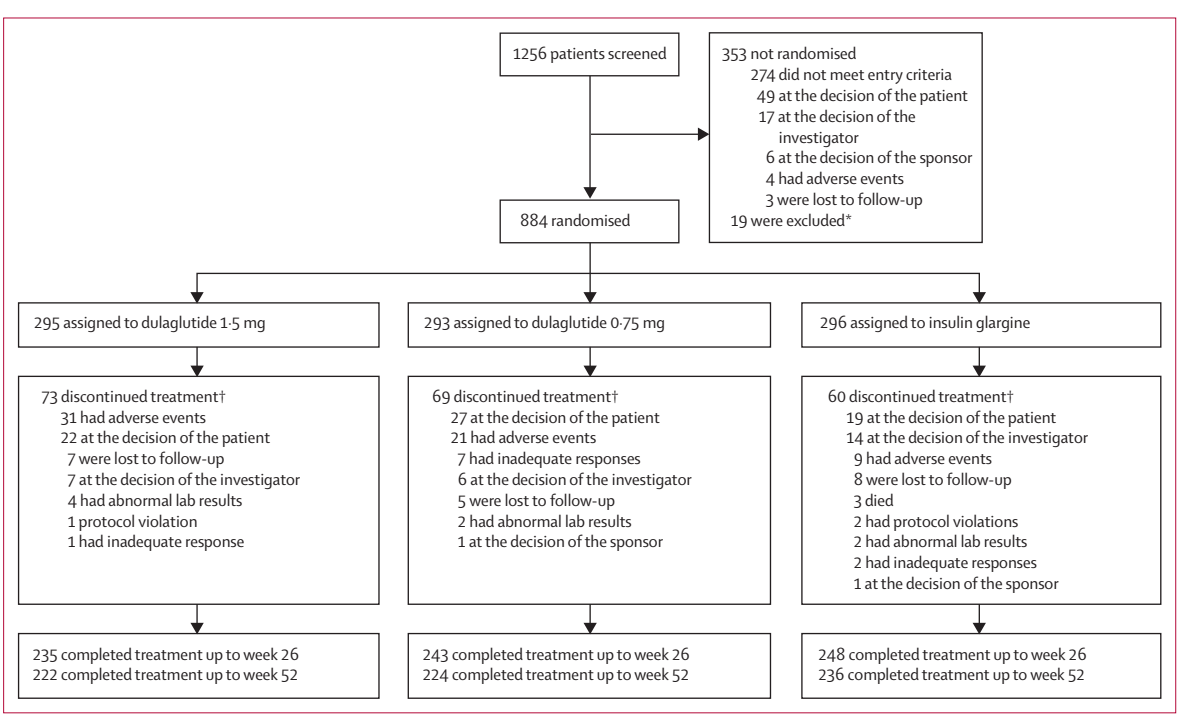

Figure 1: **Trial profile**

One patient in the dulaglutide 1·5 mg group and another in the dulaglutide 0·75 mg group died after treatment discontinuation, but while still in the study not taking the study drug. *19 screened patients at one site, eight of whom were randomised, were excluded from analysis because of Good Clinical Practice compliance issues. †Discontinuation of study treatment from week 0 to week 52. One patient in the dulaglutide 1·5 mg group, four patients in the dulaglutide 0·75 mg, and two patients in the glargine group discontinued treatment because of severe, persistent hyperglycaemia (prespecified criteria).

(–0·33 to –0·02, –1·86 mmol/mol [–3·61 to –0·22]; p=0·015) for dulaglutide 0·75 mg at 26 weeks (figure 2). At 52 weeks, changes in HbA_{1c} from baseline were greater with dulaglutide 1·5 mg (–1·48% [95% CI –1·64 to –1·32], –16·18 mmol/mol [–17·89 to –14·47]) and dulaglutide 0·75 mg (–1·42% [–1·58 to –1·26], –15·52 mmol/mol [–17·23 to –13·81]) than with glargine (–1·23% [–1·39 to –1·07], –13·45 mmol/mol [–15·16 to –11·74]; figure 2). The adjusted mean difference versus glargine was –0·25% (95% CI –0·42 to –0·07, –2·73 mmol/mol [–4·59 to –0·77]; p=0·005) for dulaglutide 1·5 mg and –0·19% (–0·37 to –0·02, –2·08 mmol/mol [–4·04 to –0·22]; p=0·014; figure 2).

	Dulaglutide 1·5 mg group (n=295)	Dulaglutide 0·75 mg group (n=293)	Glargine group (n=296)
Sex			
Male	160 (54%)	148 (50%)	165 (56%)
Female	135 (46%)	145 (50%)	131 (44%)
Age (years)	58·9 (9·6)	59·3 (9·0)	59·9 (9·1)
Age group (years)			
<65	218 (74%)	217 (74%)	206 (70%)
≥65	77 (26%)	76 (26%)	90 (30%)
Race			
American Indian or Alaska Native	16 (5%)	13 (4%)	17 (6%)
Asian	9 (3%)	12 (4%)	14 (5%)
Black or African American	32 (11%)	27 (9%)	26 (9%)
Multiple	7 (2%)	6 (2%)	7 (2%)
Native Hawaiian or other Pacific Islander	0	0	1 (<1%)
White	231 (78%)	235 (80%)	231 (78%)
Ethnic origin			
Hispanic or Latino	102 (35%)	101 (34%)	100 (34%)
Diabetes characteristics			
Disease duration (years)	12·8 (7·2)	12·4 (6·9)	13·0 (6·8)
HbA_{1c} (%)	8·46 (1·08)	8·40 (1·03)	8·53 (1·03)
HbA_{1c} (mmol/mol)	68·95 (11·8)	68·30 (11·3)	69·72 (11·3)
Weight (kg)	91·0 (18·2)	91·7 (18·0)	90·8 (18·9)
BMI (kg/m²)	32·0 (5·1)	33·1 (5·2)	32·4 (5·3)
Sitting systolic BP (mm Hg)	133·3 (16·6)	134·0 (15·9)	133·3 (17·0)
Sitting diastolic BP (mm Hg)	77·3 (9·7)	77·6 (9·0)	77·2 (10·4)
Antihyperglycaemic drugs*			
Insulin regimen			
Basal only	182 (62%)	181 (62%)	181 (61%)
Basal and prandial	113 (38%)	112 (38%)	115 (39%)
Total daily insulin dose (IU)†	55·20 (32·2)	59·11 (38·1)	53·93 (30·7)
Oral drugs	236 (80%)	237 (81%)	234 (79%)
Alpha-glucosidase inhibitors	1 (<1%)	2 (1%)	5 (2%)
Biguanides	216 (73%)	212 (72%)	214 (72%)
DPP-IV inhibitors	10 (3%)	16 (5%)	17 (6%)
Glinides	3 (1%)	1 (<1%)	4 (1%)
Sulfonylureas	80 (27%)	92 (31%)	87 (29%)
Thiazolidinediones	16 (5%)	14 (5%)	17 (6%)

Data are n (%) or mean (SD), unless otherwise indicated. HbA_{1c}=glycated haemoglobin A_{1c}. BMI=body-mass index. BP=blood pressure. DPP-IV=dipeptidyl peptidase-IV inhibitor. *Treatments used at time of study entry (screening). †At end of the stabilisation period.

Table 1: **Baseline characteristics**

At 26 weeks, the proportion of patients achieving an HbA_{1c} target of less than 7·0% (<53 mmol/mol) was significantly greater in both the dulaglutide 1·5 mg and 0·75 mg groups versus glargine (p=0·014 and p=0·010, respectively; figure 2). Compared with glargine, a significantly greater proportion of patients in the dulaglutide 1·5 mg group (p=0·027) also achieved an HbA_{1c} target of 6·5% or less (≤48 mmol/mol) at 26 weeks (figure 2). At 52 weeks, a significantly greater proportion of patients in the dulaglutide 1·5 mg group achieved HbA_{1c} less than 7·0% (<53 mmol/mol) versus glargine (p=0·0499; figure 2). The proportion of patients achieving HbA_{1c} of 6·5% or less at week 52 did not differ significantly between the dulaglutide 1·5 mg and 0·75 mg groups and the glargine group (p=0·27 and p=0·62, respectively; figure 2). For the composite endpoints assessing the proportion of patients achieving HbA_{1c} less than 7·0% without documented symptomatic hypoglycaemia and, separately, without nocturnal or severe hypoglycaemia, alone or in combination with no weight gain, significantly more patients met the criteria in the dulalgutide 1·5 mg group than the glargine group at both weeks 26 and 52 (all p<0·05; appendix).

The reductions in adjusted mean fasting serum glucose from baseline to week 26 were significantly greater with glargine (–1·58 mmol/L [95% CI –1·97 to –1·19]) than with dulaglutide 1·5 mg (–0·27 mmol/L [–0·66 to 0·12]; p<0·0001) or dulaglutide 0·75 mg (0·22 mmol/L [–0·17 to 0·61]; p<0·0001); results were similar at week 52 (both p<0·0001; figure 2).

The self-monitored plasma glucose values (8-point daily profile) at 26 weeks decreased at each timepoint compared with baseline in all groups (figure 2, appendix). Reductions in plasma glucose were significantly greater with glargine than with both dulaglutide doses at 0300 h (5 h after bedtime) and before breakfast, and than dulaglutide 0·75 mg 2 h after the morning meal (all p<0·020; appendix). Decreases in plasma glucose were significantly greater with dulaglutide doses than with glargine at the 2 h post-midday meal, pre-evening meal (except for dulaglutide 0·75 mg *vs* glargine), 2 h post-evening meal, and at bedtime (all p<0·050). The reductions in the mean of all fasting and pre-meal plasma glucose were significantly greater with glargine, whereas the decrease in the mean of all postprandial glucose values was significantly greater with dulaglutide 1·5 mg (figure 2). The decrease in mean nocturnal plasma glucose was significantly greater with glargine than with the dulaglutide 1·5 mg or 0·75 mg doses; daytime mean reductions were similar between groups (appendix). Results were similar at 52 weeks (appendix). At weeks 26 and 52, the mean dose of total daily insulin was roughly 30% lower in patients receiving dulaglutide than in those receiving glargine (table 2). The mean daily lispro dose was roughly 30% lower in patients in the glargine group (table 2).

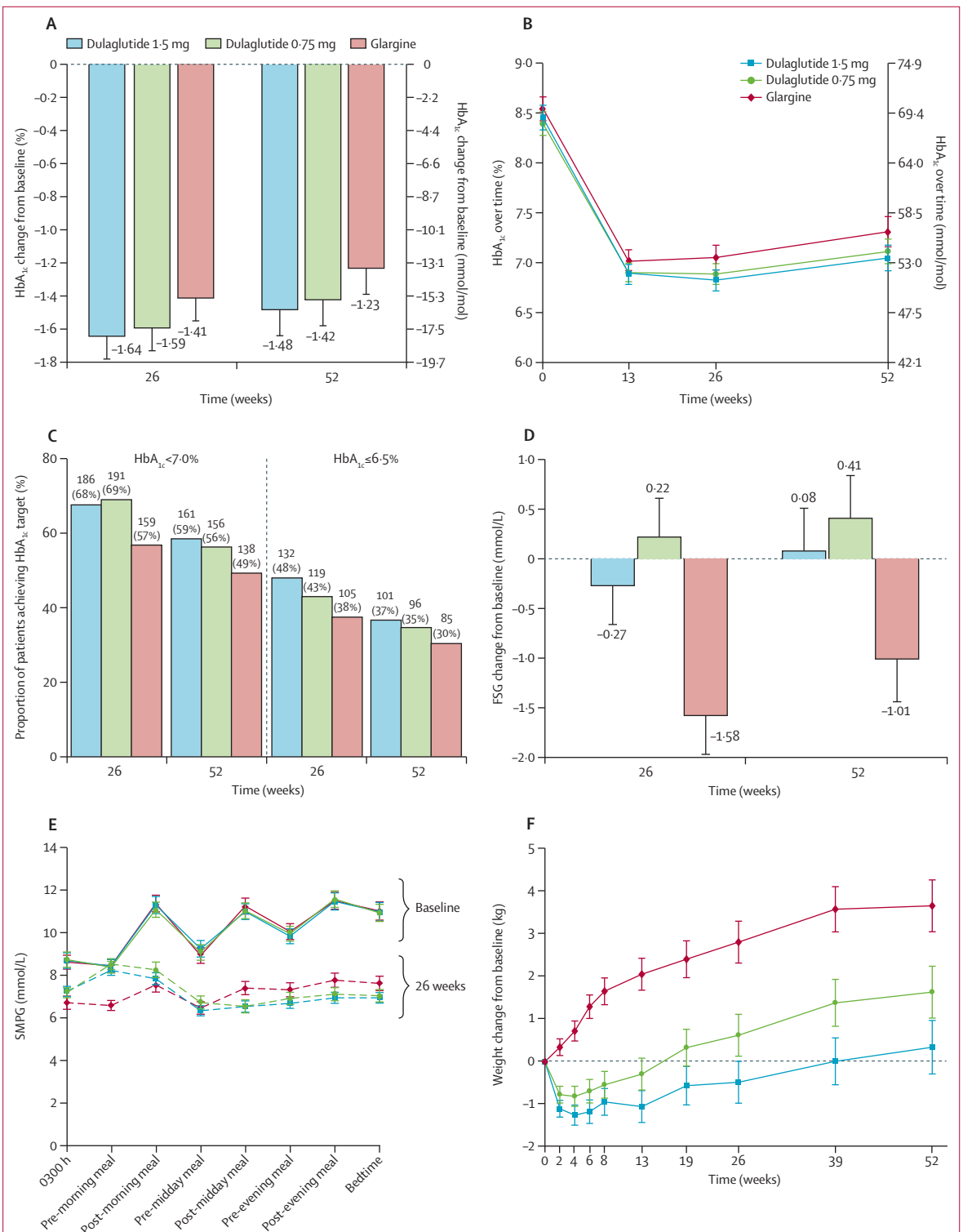

***Figure 2*: Efficacy variables**

(A) Least-squares mean change in HbA_{1c} from baseline to weeks 26 and 52 weeks and (B) over time. (C) Proportion of patients achieving HbA_{1c} targets; values above the bars are n (%). (D) Least-squares mean change in FSG from baseline. (E) Baseline and 26 week 8-point SMPG profiles. (F) Change in weight over time. Error bars show 95% CIs. HbA_{1c}=glycated haemoglobin A_{1c}. FSG=fasting serum glucose. SMPG=self-monitored plasma glucose.

	N	Total daily glargine	Total daily lispro	p value	Total daily combined
Units					
Week 26					
Dulaglutide 1·5 mg	244	..	93·24 (83·45–103·03; 100%)	<0·0001	93·24 (83·45–103·03)
Dulaglutide 0·75 mg	251	..	96·69 (89·00–104·38; 100%)	<0·0001	96·69 (89·00–104·38)
Glargine	254	64·48 (59·53–69·43; 49·8%)	67·79 (62·31–73·27; 50·4%)	..	132·00 (122·28–141·72)
Week 52					
Dulaglutide 1·5 mg	224	..	88·15 (79·91–96·39; 100%)	0·0006	88·15 (79·91–96·39)
Dulaglutide 0·75 mg	227	..	95·00 (86·20–103·80; 100%)	<0·0001	95·00 (86·20–103·80)
Glargine	238	64·07 (59·17–68·97; 50·0%)	69·12 (62·89–75·35; 50·0%)	..	133·19 (122·93–143·45)
Units per kg					
Week 26					
Dulaglutide 1·5 mg	244	..	0·99 (0·90–1·08; 100%)	<0·0001	0·99 (0·90–1·08)
Dulaglutide 0·75 mg	251	..	1·03 (0·96–1·10; 100%)	<0·0001	1·03 (0·96–1·10)
Glargine	254	0·68 (0·63–0·73; 49·8%)	0·72 (0·67–0·77; 50·4%)		1·39 (1·30–1·48)
Week 52					
Dulaglutide 1·5 mg	224	..	0·93 (0·86–1·00; 100%)	<0·0001	0·93 (0·86–1·00)
Dulaglutide 0·75 mg	227	..	0·99 (0·92–1·06; 100%)	<0·0001	0·99 (0·92–1·06)
Glargine	238	0·68 (0·63–0·73; 50·1%)	0·73 (0·67–0·79; 49·9%)	..	1·41 (1·31–1·51)

Data are mean (95% CI; total daily insulin dose [%]) or mean (95% CI), unless otherwise indicated.

Table 2: **Daily insulin dose from baseline to 52 weeks**

The adjusted mean changes in bodyweight at 26 weeks were –0·87 kg (95% CI –1·40 to –0·34) in the dulaglutide 1·5 mg group, 0·18 kg (–0·35 to 0·71) in the dulaglutide 0·75 mg group, and 2·33 kg (1·80–2·86) in the glargine group (figure 2). The differences between the dulaglutide and glargine groups were significant (all p<0·0001) and similar differences were noted at 52 weeks (figure 2). Between-group differences for change in BMI were consistent with weight findings (data not shown). The increases in HDL cholesterol were significantly greater in the dulaglutide 1·5 mg (p=0·0002) and 0·75 mg groups (p<0·0001) versus glargine at 52 weeks (appendix). Changes in other lipid analytes did not differ significantly between groups (appendix).

The results of patient-reported outcomes showed that perceived health status and ability to do physical activities of daily living decreased despite reductions in HbA_{1c} in all treatment groups (data not shown). In the dulaglutide 1·5 mg group, patients reported an improvement in effect of weight on self-perception compared with patients in the glargine group (data not shown). No other between-group differences were noted for patient-reported outcomes (data not shown).

Five (<1%) patients died after randomisation because of septicaemia (n=1 in the dulaglutide 1·5 mg group); pneumonia (n=1 in the dulaglutide 0·75 mg group); cardiogenic shock; ventricular fibrillation; and an unknown cause (n=3 in the glargine group; table 3). The incidence of serious adverse events was significantly lower in the dulaglutide 1·5 mg group than in the glargine group and similar in the dulaglutide 0·75 mg group (table 3). Compared with glargine, the incidence of adverse events was significantly higher with dulaglutide 0·75 mg and similar with dulaglutide 1·5 mg (table 3). The most frequent adverse events, arising significantly more often with dulaglutide than glargine, were nausea, diarrhoea, and vomiting (table 3). Gastrointestinal events were mostly mild to moderate and most resolved within the first 4–6 weeks. The number of patients who discontinued the study because of an adverse event or death was 21 (7%) in the dulaglutide 1·5 mg group, 14 (5%) in the dulaglutide 0·75 mg group, and 11 (4%) in the glargine group (table 3). Nausea was the most common adverse event leading to discontinuation, affecting ten patients (n=5 in each dulaglutide group).

Incidence of total hypoglycaemia was similar in the three groups; the rate of total hypoglycaemia was significantly lower with dulaglutide 1·5 mg versus glargine at both weeks 26 (p<0·0001) and 52 (p=0·0008; appendix). Incidence and rate of nocturnal hypoglycaemia were also significantly lower with dulaglutide versus glargine at weeks 26 (all p<0·0001, except dulaglutide 0·75 mg [p=0·0004]) and 52 (all p<0·0001, except dulaglutide 0·75 mg [p=0·0007]; appendix). Overall, 48 severe hypoglycaemia events were reported, with 11 events in ten patients in the dulaglutide 1·5 mg group, 15 events in seven patients in the dulaglutide 0·75 mg group, and 22 events in 15 patients in the glargine group.

Treatment with dulaglutide 1·5 mg was associated with a decrease in systolic blood pressure compared with an increase in systolic blood pressure with glargine (adjusted mean difference of roughly 2–3 mm Hg; table 3). The differences were significant at each visit (all p<0·05), except 52 weeks. Changes in diastolic blood pressure did not differ significantly between groups (table 3). Both dulaglutide doses significantly increased heart rate

	Dulaglutide 1·5 mg group (n=295)	p value	Dulaglutide 0·75 mg group (n=293)	p value	Glargine group (n=296)
Death	1 (<1%)	..	1 (<1%)	..	3 (1%)
Serious adverse events*	27 (9%)	0·0013	44 (15%)	0·29	54 (18%)
Hypoglycaemia†	10 (3%)	0·31	8 (3%)	0·14	15 (5·1%)
Pneumonia	1 (<1%)	1·0	4 (1%)	0·21	1 (<1%)
Angina pectoris	1 (<1%)	0·62	0	0·25	3 (1%)
Cellulitis	0	0·50	2 (1%)	1·0	2 (1%)
Coronary artery disease	1 (<1%)	0·62	0	0·25	3 (1%)
Treatment-emergent adverse events (patients with ≥1 event)	217 (74%)	0·29	230 (78%)	p=0·014	206 (70%)
Treatment-emergent adverse events (reported by ≥5% of patients in any group)					
Gastrointestinal events					
Nausea	76 (26%)	<0·0001	52 (18%)	<0·0001	10 (3%)
Diarrhoea	49 (17%)	<0·0001	46 (16%)	0·0002	18 (6%)
Vomiting	36 (12%)	<0·0001	31 (11%)	<0·0001	5 (2%)
Dyspepsia	27 (9%)	<0·0001	10 (3%)	0·006	1 (<1%)
Infections and infestations					
Nasopharyngitis	20 (7%)	0·084	32 (11%)	0·97	32 (11%)
Influenza	15 (5%)	0·69	19 (6%)	0·26	13 (4%)
Urinary tract infection	10 (3%)	0·31	17 (6%)	0·69	15 (5%)
Bronchitis	8 (3%)	0·067	12 (4%)	0·36	17 (6%)
Other adverse events					
Headache	17 (6%)	0·62	26 (9%)	0·34	20 (7%)
Decreased appetite	27 (9%)	<0·0001	18 (6%)	<0·0001	0
Arthralgia	8 (3%)	0·14	13 (4%)	0·72	15 (5%)
Hypoglycaemia	10 (3%)	0·31	8 (3%)	0·14	15 (5%)
Oedema peripheral	7 (2%)	0·62	15 (5%)	0·20	9 (3%)
Adverse events of special interest‡					
Adjudicated cardiovascular events	5 (2%)	NA	6 (2%)	NA	12 (4%)
Hypersensitivity events	1 (<1%)	NA	5 (2%)	NA	1 (<1%)
Injection-site reaction	1 (<1%)	NA	4 (1%)	NA	0
Discontinuation of study treatment because of death or adverse events‡	31 (11%)	NA	22 (8%)	NA	12 (4%)
Discontinuation of study because of death or adverse events‡	21 (7%)	NA	14 (5%)	NA	11 (4%)
Mean change (95% CI) from baseline in vital signs					
Systolic BP (mm Hg)	−0·26 (−2·10 to 1·58)	0·066	1·04 (−0·78 to 2·86)	0·44	1·98 (0·18 to 3·78)
Diastolic BP (mm Hg)	−0·01 (−1·13 to 1·11)	0·65	0·15 (−0·97 to 1·27)	0·50	−0·34 (−1·44 to 0·76)
Heart rate (beats per min)	2·38 (1·26 to 3·50)	0·047	2·27 (1·15 to 3·39)	0·066	0·93 (−0·19 to 2·05)
Treatment-emergent dulaglutide antidrug antibodies (both groups combined)§					
Dulaglutide antidrug antibodies	..	9 (2%)	..	..	..
Neutralising dulaglutide	..	6 (1%)	..	..	..
Cross-reactive native-sequence GLP-1	..	4 (1%)	..	..	..
Neutralising native-sequence GLP-1	..	1 (<1%)	..	..	..

Data are n (%), unless otherwise indicated. p values are for dulaglutide *vs* insulin glargine. Hypersensitivity events were assessed with specific standardised MedDRA queries (anaphylactic reaction, angioedema, or severe cutaneous adverse reaction narrow terms). Injection-site reaction was based on a Lilly search category that included specific MedDRA Preferred Terms subsidiary to the MedDRA HLT for injection-site reaction. NA=not applicable. BP=blood pressure. GLP-1=glucagon-like peptide-1. *Reported by at least 0·5% patients across all treatment groups. †The study protocol required that severe hypoglycaemia be reported as a serious adverse event; this requirement might have affected the incidence of these categories of reported events. ‡These outcomes were summarised only, no statistical comparisons were done. §Results for both dulaglutide groups combined for all post-baseline observations including follow-up. The appendix shows pancreatic enzyme data.

Table 3: **Adverse events, changes from baseline in vital signs, and treatment-emergent dulaglutide antidrug antibodies from baseline to 52 weeks**

(adjusted mean difference 1·5–3·0 beats per min) versus glargine (table 3). 23 (3%) patients had at least one cardiovascular event confirmed by adjudication (table 3). There were two fatal cardiovascular events, both in the glargine group.

Median increases in pancreatic enzymes were significantly greater in patients in the dulaglutide groups than in those in the glargine group (appendix). The incidence of clinically relevant increases in lipase (≥3×ULN) was numerically higher with dulaglutide 1·5 mg (n=8) and 0·75 mg (n=5) than with glargine (n=3). Incidence of values of 3×ULN or more for total or pancreatic amylase did not differ significantly between groups. No events of adjudicated pancreatitis or pancreatic cancer were noted. Changes in calcitonin concentrations did not differ significantly between groups during the treatment period (appendix), with no malignant thyroid neoplasms reported. Dulaglutide antidrug antibodies were reported in nine (2%) patients receiving dulaglutide (table 3). We recorded seven systemic hypersensitivity adverse events (table 3), none of which was classified as severe: urticaria (n=1 in the dulaglutide 1·5 mg group, n=2 in the dulaglutide 0·75 mg group, n=1 in the glargine group), and unspecified hypersensitivity (n=3 in the dulaglutide 0·75 mg group). Five (1%) patients reported injection-site reactions (table 3). No patient with dulaglutide antidrug antibodies reported hypersensitivity events.

Discussion

Treatment with dulaglutide 1·5 mg resulted in significantly greater reductions in HbA_{1c} than did treatment with glargine after 26 weeks. Despite this difference in HbA_{1c} reduction, mean weight decreased by roughly 0·9 kg with dulaglutide 1·5 mg versus a 2·3 kg gain with glargine, and risk of hypoglycaemia was significantly lower with dulaglutide 1·5 mg. We recorded similar results at 52 weeks. The effect of dulaglutide 0·75 mg on HbA_{1c} was likewise significantly greater than with glargine, with less weight gain, but risk of hypoglycaemia did not differ between patients in these groups.

Our results clearly show a clinically relevant glucose-lowering effect with all studied treatments. Both dulaglutide doses had a significantly greater effect than glargine on HbA_{1c} (at both 26 and 52 weeks), with a higher proportion of patients in the dulaglutide 1·5 mg group achieving HbA_{1c} less than 7·0% (<53 mmol/mol). In the HARMONY-6 trial[7] in which a glargine–albiglutide combination was compared with a glargine–lispro regimen, glucose-lowering effects were similar between treatments, despite a fairly modest reduction in HbA_{1c} in the basal–bolus group (–0·66%), potentially related to the insufficient dose of total daily insulin (about 80 units). The outcome of the 4B trial,[8] which compared glargine–exenatide twice daily with glargine–lispro regimens, was similar to that of HARMONY-6 with respect to reduction in HbA_{1c}, despite a higher dose of total daily insulin in the basal–bolus group (94 units). Comparatively in the present study, glargine combined with lispro, with a mean total daily insulin dose of more than 132 units, had a greater effect on change in HbA_{1c} (–1·41%), and yet dulaglutide plus lispro still resulted in a significantly greater reduction in HbA_{1c}. These results provide support for once-weekly dulaglutide, in combination with prandial insulin, as an effective alternative treatment for patients with type 2 diabetes who cannot achieve glycaemic targets with one or two daily insulin injections.

These results might also address concerns about the mechanistic ability of a GLP-1 receptor agonist to produce an adequate response in a patient population with type 2 diabetes of longer duration and presumably diminished β-cell function or mass.[20,21] Indeed, our findings confirm that dulaglutide is effective in this population, with a mean diabetes duration of more than 12 years, as shown by an improvement in glycaemic control throughout the 24 h profile, and a daily insulin requirement that was lower (about 40 units) with the dulaglutide–lispro combination than with the glargine–lispro combination.

Glucose-lowering results should always be interpreted in the context of hypoglycaemia risk and insulin dose. Compared with glargine, dulaglutide 1·5 mg was associated with a lower risk of hypoglycaemia and fewer severe hypoglycaemic events, despite the significantly greater decrease in HbA_{1c} and higher lispro doses. This regimen also resulted in a significantly higher proportion of patients reaching the HbA_{1c} target of less than 7·0% without having nocturnal or severe hypoglycaemia, or without having documented symptomatic hypoglycaemia. Patients in the glargine group had a roughly 30% higher dose of total daily insulin, and those in the dulaglutide groups had a roughly 30% higher mean lispro dose. Importantly, the higher lispro dose in the dulaglutide 1·5 mg group was associated with lower daytime risk of hypoglycaemia, despite lower glycaemia for most of the day and greater HbA_{1c} reduction. Therefore, differences in lispro dosing are unlikely to explain the outcome of the trial. These results suggest that the risk of iatrogenic hyperinsulinaemia and consequent hypoglycaemia is lower with dulaglutide than with glargine, allowing for lispro dose titration that better meets patients' needs. These differences between the treatments might be related to the mechanisms of action of dulaglutide, including improvement in glucose-dependent insulin secretion.[22]

Bodyweight decreased in patients in the dulaglutide 1·5 mg group and slightly increased in those in the 0·75 mg group. These changes differed significantly from the increase in weight noted with glargine, with clinically relevant between-group differences. This result could be explained by the known effect of GLP-1 receptor agonists on bodyweight, together with lower total insulin dosing in the two dulaglutide groups. The significant increase in HDL cholesterol with dulaglutide might represent an additional benefit of the dulaglutide–lispro regimen.

Panel: Research in context

Systematic review

We searched PubMed between Jan 1, 2005, to June 30, 2014, with the terms "insulin and exenatide", "insulin and liraglutide", "insulin and lixisenatide", and "insulin and albiglutide". We excluded non-English references. We identified six randomised, controlled, efficacy and safety trials in which a once-weekly glucagon-like peptide-1 (GLP-1) receptor agonist was combined with basal insulin. Only two of these trials included an active comparator group (albiglutide–basal insulin *vs* basal–bolus [HARMONY-6[7]] and exenatide twice daily *vs* mealtime insulin lispro combined with insulin glargine [the 4B trial[8]]). No trial combined a GLP-1 receptor agonist with rapidly acting prandial insulin.[8,31]

Interpretation

Treatment with once-weekly dulaglutide 1·5 mg resulted in a significantly greater change in glycated haemoglobin A_{1c} (HbA_{1c}) from baseline to 26 weeks than did treatment with basal insulin glargine, both in combination with prandial lispro. Patients given dulaglutide 1·5 mg also had a significant weight benefit, lower risk of hypoglycaemia, and needed 30% less insulin during the day because of the absence of basal insulin, but had higher lispro doses than those given glargine. Dulaglutide 0·75 mg likewise had a significantly greater effect on change in HbA_{1c} than did glargine, with less weight gain, but with a similar risk of hypoglycaemia. Differences between the treatment groups remained similar after 52 weeks of treatment. AWARD-4 is the first trial to show how the combination of a GLP-1 receptor agonist with prandial insulin compares with a basal–bolus insulin regimen. These findings could help inform treatment decisions for patients with type 2 diabetes who are unable to achieve their target glucose control with conventional insulin treatment.

Overall, the safety profile of dulaglutide was consistent with previous reports,[22–26] with the most commonly reported adverse events being nausea, diarrhoea, and vomiting. These events were transient and rarely resulted in treatment discontinuation. AWARD-4 confirms findings from several recently published reports describing an increase in the mean concentration of pancreatic enzymes with different glucose-lowering drugs, including those that act via a GLP-1-based mechanism.[9,10,13,27–30] Whether this effect is non-physiological or physiological remains unknown, but that no events of acute pancreatitis or pancreatic neoplasms were reported in our study is reassuring.

This trial has several important limitations. The choice of comparator—intensive basal–bolus insulin treatment—is only one of the recommended treatment options for the patient population included in this trial, and these results cannot be extrapolated to other comparative regimens. As discussed, although we believe that dulaglutide in combination with lispro showed an acceptable risk–benefit profile, we could not fully account for the effect of the difference in lispro doses between groups. Inherent to studies that include an insulin regimen, we could not mask treatment allocation because of the need to titrate insulin doses, which would be very difficult if the patient did not know which treatment they were prescribed.

The results of AWARD-4 are relevant for patients who are already using one or two doses of basal or basal–prandial insulin, and yet are unable to reach glycaemic targets (panel). These patients are often treated by intensification of insulin treatment to a basal–bolus regimen. However, the combination of once-weekly dulaglutide with prandial lispro offers an additional option, with an improved risk–benefit profile compared with basal–bolus insulin treatment.

Contributors

LB, JJ, JG, and VW were participated in data collection. HJ, JLF, and ZM prepared the first draft of the manuscript. ZM wrote the research in context panel. JLF and ZM were responsible for medical oversight during the trial. HJ was responsible for the statistical considerations in the analysis and trial design. All authors participated in reviewing and interpreting the data and providing comments and revisions to the manuscript. All authors approved the final version of the manuscript and take full responsibility for the content.

Declaration of interests

LB has served as a consultant and author for Amylin Pharmaceuticals, Eisai, GlaxoSmithKline, Janssen Pharmaceuticals, Merck, Novo Nordisk, Pfizer, Sanofi, and Santarus; has been on a speaker's bureau for Amylin Pharmaceuticals, Bristol-Myers Squibb/AstraZeneca, Janssen Pharmaceuticals, Johnson & Johnson Diabetes Institute, Merck, Novo Nordisk, Sanofi, Santarus, and Vivus; and has received research support to his institution from Eli Lilly and Company, Novo Nordisk, and Sanofi. JJ has served on advisory panels for Roche Diagnostics, Janssen Pharmaceuticals, Novo Nordisk, Eli Lilly and Company, Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb Company, and Medtronic; has received research support from Novo Nordisk; and has been on a speaker's bureau for AstraZeneca, Pfizer, Eli Lilly and Company, Novo Nordisk, and Boehringer Ingelheim. JG has served as a consultant and author for Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb Company, Eli Lilly and Company, and Novo Nordisk; and has received research support from Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb Company, Eli Lilly and Company, GlaxoSmithKline, and Novo Nordisk. VW has served as a consultant and author for Eli Lilly and Company, Novo Nordisk, Sanofi, Merck, AstraZeneca Pharmaceuticals, Bristol-Myers Squibb Company, Takeda Pharmaceutical Company, and Boehringer Ingelheim Pharmaceuticals; and been on a speaker's bureau for Eli Lilly and Company, Novo Nordisk, Sanofi, Merck, AstraZeneca Pharmaceuticals, Bristol-Myers Squibb Company, Takeda Pharmaceutical Company, and Boehringer Ingelheim Pharmaceuticals. HJ, JLF, and ZM are employees of Eli Lilly and Company and own stocks and shares.

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References

1 Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009; **32:** 193–203.

2 Garber AJ, Abrahamson MJ, Barzilay JI, et al. AACE comprehensive diabetes management algorithm 2013. *Endocr Pract* 2013; **19:** 327–36.

3 Meneghini LF, Orozco-Beltran D, Khunti K et al. Weight beneficial treatments for type 2 diabetes. *J Clin Endocrinol Metab* 2011; **96:** 3337–53.

4 Rosenstock J, Ahmann AJ, Colon G, Scism-Bacon J, Jiang H, Martin S. Advancing insulin therapy in type 2 diabetes previously treated with glargine plus oral agents: prandial premixed (insulin lispro protamine suspension/lispro) versus basal/bolus (glargine/lispro) therapy. *Diabetes Care* 2008; **31:** 20–25.

5 Hollander P, Cooper J, Bregnhoj J, Pedersen CB. A 52-week, multinational, open-label, parallel-group, noninferiority, treat-to-target trial comparing insulin detemir with insulin glargine in a basal-bolus regimen with mealtime insulin aspart in patients with type 2 diabetes. *Clin Ther* 2008; **30:** 1976–87.

6 Raskin P, Gylvin T, Weng W, Chaykin L. Comparison of insulin detemir and insulin glargine using a basal-bolus regimen in a randomized, controlled clinical study in patients with type 2 diabetes. *Diabetes Metab Res Rev* 2009; **25:** 542–48.

7 Rosenstock J, Ahren B, Chow FC, Fonseca V, Gross J, Ratner R. Once-weekly GLP-1 receptor agonist albiglutide vs titrated prandial lispro added on to titrated basal insulin glargine in type 2 diabetes (T2D) uncontrolled on glargine plus oral agents: similar glycemic control with weight loss and less hypoglycemia. *Diabetes* 2012; **61** (suppl 1)**:** A15.

8 Diamant M, Nauck MA, Shaqinian R, et al. Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes. *Diabetes Care* 2014; **37:** 2763–73.

9 Wysham CH, Blevins T, Arakaki R, et al. Efficacy and safety of dulaglutide added on to pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). *Diabetes Care* 2014; **37:** 2159–67.

10 Umpierrez GE, Povedano ST, Manghi FP, Shurzinske L, Pechtner V. Efficacy and safety of dulaglutide monotherapy vs metformin in type 2 diabetes in a randomized controlled trial (AWARD-3). *Diabetes Care* 2014; **37:** 2168–76.

11 Weinstock R, Umpierrez G, Guerci B, et al. Safety and Efficacy of Dulaglutide vs Sitagliptin after 104 Weeks in Type 2 Diabetes (AWARD-5). American Diabetes Association 73rd annual meeting; Chicago, IL, USA; June 23–21, 2013. 1004-P (abstr).

12 Skrivanek Z, Gaydos BL, Chien JY, et al. Dose-finding results in an adaptive, seamless, randomised trial of once weekly dulaglutide combined with metformin in type 2 diabetes (AWARD-5). *Diabetes Obes Metab* 2014; **16:** 748–56.

13 Nauck M, Weinstock RS, Umpierrez GE, Guerci B, Skrivanek Z, Milicevic Z. Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes (AWARD-5). *Diabetes Care* 2014; **37:** 2149–58.

14 World Medical Association. World Medical Association declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. *JAMA* 1997; **277:** 925–26.

15 Riddle MC, Rosenstock J, Gerich J. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 2003; **26:** 3080–86.

16 Bergenstal RM, Johnson M, Powers MA, et al. Adjust to target in type 2 diabetes: comparison of a simple algorithm with carbohydrate counting for adjustment of mealtime insulin glulisine. *Diabetes Care* 2008; **31:** 1305–10.

17 American Diabetes Association. Standards of medical care in diabetes—2010. *Diabetes Care* 2010; **33** (suppl 1)**:** S11–61.

18 American Diabetes Association Workgroup on Hypoglycemia. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. *Diabetes Care* 2005; **28:** 1245–49.

19 Dmitrienko A, Tamhane AC, Wiens BL. General multistage gatekeeping procedures. *Biom J* 2008; **50:** 667–77.

20 Porte D Jr, Kahn SE. Beta-cell dysfunction and failure in type 2 diabetes: potential mechanisms. *Diabetes* 2001; **50** (suppl 1)**:** S160–63.

21 Holst JJ. The physiology of glucagon-like peptide 1. *Physiol Rev* 2007; **87:** 1409–39.

22 Umpierrez GE, Blevins T, Rosenstock J, Cheng C, Anderson JH, Bastyr EJ 3rd. The effects of LY2189265, a long-acting glucagon-like peptide-1 analogue, in a randomized, placebo-controlled, double-blind study of overweight/obese patients with type 2 diabetes: the EGO study. *Diabetes Obes Metab* 2011; **13:** 418–25.

23 Grunberger G, Chang A, Garcia SG, Botros FT, Bsharat R, Milicevic Z. Monotherapy with the once-weekly GLP-1 analogue dulaglutide for 12 weeks in patients with Type 2 diabetes: dose-dependent effects on glycaemic control in a randomized, double-blind, placebo-controlled study. *Diabet Med* 2012; **29:** 1260–67.

24 Moretto TJ, Milton DR, Ridge TD, et al. Efficacy and tolerability of exenatide monotherapy over 24 weeks in antidiabetic drug-naive patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, parallel-group study. *Clin Ther* 2008; **30:** 1448–60.

25 Drucker DJ, Buse JB, Taylor K, et al. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. *Lancet* 2008; **372:** 1240–50.

26 Garber A, Henry R, Ratner R, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet* 2009; **373:** 473–81.

27 Dungan KM, Povedano ST, Forst T, et al. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. *Lancet* 2014; **384:** 1349–57.

28 Steinberg W, DeVries JH, Wadden TA, et al. Longitudinal monitoring of lipase and amylase in adults with type 2 diabetes and obesity: evidence from two phase 3 randomized clinical trials with the once-daily GLP-1 analog liraglutide. *Gastroenterology* 2012; **142** (suppl 1)**:** S850–51.

29 Blevins T, Pullman J, Malloy J, et al. DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with type 2 diabetes. *J Clin Endocrinol Metab* 2011; **96:** 1301–10.

30 DeVries JH, Bain SC, Rodbard HW, et al. Sequential intensification of metformin treatment in type 2 diabetes with liraglutide followed by randomized addition of basal insulin prompted by A1C targets. *Diabetes Care* 2012; **35:** 1446–54.

31 Rosenstock J, Fonseca VA, Gross JL, et al. Advancing basal insulin replacement in Type 2 diabetes inadequately controlled with a comparison of adding albiglutide, a weekly GLP-1 receptor agonist, versus thrice-daily prandial insulin Lispro. *Diabetes Care* 2014; **37:** 2317–25.