# Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial

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## Summary

**Background** Many antihyperglycaemic drugs, including insulin, are primarily cleared by the kidneys, restricting treatment options for patients with kidney disease. Dulaglutide is a long-acting glucagon-like peptide-1 receptor agonist that is not cleared by the kidneys, and confers a lower risk of hypoglycaemia than does insulin. We assessed the efficacy and safety of dulaglutide in patients with type 2 diabetes and moderate-to-severe chronic kidney disease.

**Methods** AWARD-7 was a multicentre, open-label trial done at 99 sites in nine countries. Eligible patients were adults with type 2 diabetes and moderate-to-severe chronic kidney disease (stages 3–4), with an $HbA_{1c}$ of 7·5–10·5%, and who were being treated with insulin or insulin plus an oral antihyperglycaemic drug and were taking a maximum tolerated dose of an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker. Participants were randomly assigned (1:1:1) by use of a computer-generated random sequence with an interactive response system to once-weekly injectable dulaglutide 1·5 mg, once-weekly dulaglutide 0·75 mg, or daily insulin glargine as basal therapy, all in combination with insulin lispro, for 52 weeks. Insulin glargine and lispro doses were titrated as per an adjustment algorithm; dulaglutide doses were masked to participants and investigators. The primary outcome was $HbA_{1c}$ at 26 weeks, with a 0·4% non-inferiority margin. Secondary outcomes included estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (UACR). The primary analysis population was all randomly assigned patients who received at least one dose of study treatment and had at least one post-randomisation $HbA_{1c}$ measurement. The safety population was all patients who received at least one dose of study treatment and had any post-dose data. This study is registered with ClinicalTrials.gov, number NCT01621178.

**Findings** Between Aug 15, 2012, and Nov 30, 2015, 577 patients were randomly assigned, 193 to dulaglutide 1·5 mg, 190 to dulaglutide 0·75 mg, and 194 to insulin glargine. The effects on $HbA_{1c}$ change at 26 weeks of dulaglutide 1·5 mg and 0·75 mg were non-inferior to those of insulin glargine (least squares mean [LSM] –1·2% [SE 0·1] with dulaglutide 1·5 mg [183 patients]; –1·1% [0·1] with dulaglutide 0·75 mg [180 patients]; –1·1% [0·1] with insulin glargine [186 patients]; one-sided p≤0·0001 for both dulaglutide doses *vs* insulin glargine). The differences in $HbA_{1c}$ concentration at 26 weeks between dulaglutide and insulin glargine treatments were LSM difference –0·05% (95% CI –0·26 to 0·15, p<0·0001) with dulaglutide 1·5 mg and 0·02% (–0·18 to –0·22, p=0·0001) with dulaglutide 0·75 mg. $HbA_{1c}$-lowering effects persisted to 52 weeks (LSM –1·1% [SE 0·1] with dulaglutide 1·5 mg; –1·1% [0·1] with dulaglutide 0·75 mg; –1·0% [0·1] with insulin glargine). At 52 weeks, eGFR was higher with dulaglutide 1·5 mg (Chronic Kidney Disease Epidemiology Collaboration equation by cystatin C geometric LSM 34·0 mL/min per 1·73 m² [SE 0·7]; p=0·005 *vs* insulin glargine) and dulaglutide 0·75 mg (33·8 mL/min per 1·73 m² [0·7]; p=0·009 *vs* insulin glargine) than with insulin glargine (31·3 mL/min per 1·73 m² [0·7]). At 52 weeks, the effects of dulaglutide 1·5 mg and 0·75 mg on UACR reduction were not significantly different from that of insulin glargine (LSM –22·5% [95% CI –35·1 to –7·5] with dulaglutide 1·5 mg; –20·1% [–33·1 to –4·6] with dulaglutide 0·75 mg; –13·0% [–27·1 to 3·9] with insulin glargine). Proportions of patients with any serious adverse events were similar across groups (20% [38 of 192] with dulaglutide 1·5 mg, 24% [45 of 190] with dulaglutide 0·75 mg, and 27% [52 of 194] with insulin glargine). Dulaglutide was associated with higher rates of nausea (20% [38 of 192] with dulaglutide 1·5 mg and 14% [27 of 190] with 0·75 mg, *vs* 5% [nine of 194] with insulin glargine) and diarrhoea (17% [33 of 192] with dulaglutide 1·5 mg and 16% [30 of 190] with 0·75 mg, *vs* 7% [14 of 194] with insulin glargine) and lower rates of symptomatic hypoglycaemia (4·4 events per patient per year with dulaglutide 1·5 mg and 4·3 with dulaglutide 0·75 mg, *vs* 9·6 with insulin glargine). End-stage renal disease occurred in 38 participants: eight (4%) of 192 with dulaglutide 1·5 mg, 14 (7%) of 190 with dulaglutide 0·75 mg, and 16 (8%) of 194 with insulin glargine.

**Interpretation** In patients with type 2 diabetes and moderate-to-severe chronic kidney disease, once-weekly dulaglutide produced glycaemic control similar to that achieved with insulin glargine, with reduced decline in eGFR. Dulaglutide seems to be safe to use to achieve glycaemic control in patients with moderate-to-severe chronic kidney disease.

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## Research in context

### Evidence before this study

We searched PubMed on Dec 5, 2017, with the terms "liraglutide", "exenatide", "albiglutide", "lixisenatide", "semaglutide", "dulaglutide", and "type 2 diabetes" and "chronic kidney disease", with no date or trial duration restrictions. Studies not reported in English were excluded. Studies including prespecified kidney outcome data were identified. Composite kidney outcomes were reported in a prespecified analysis of the LEADER cardiovascular outcome trial, in which the glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide was compared with placebo in addition to standard care. The trial included 9340 patients with type 2 diabetes and high cardiovascular risk, including about 220 patients with an estimated glomerular filtration rate (eGFR) lower than 30 mL/min per 1·73 $m^2$. In this study, the slope of eGFR decline was attenuated with liraglutide in patients with eGFR of 30–59 mL/min per 1·73 $m^2$.

### Added value of this study

To our knowledge, AWARD-7 is the first study of a GLP-1 receptor agonist to specifically enrol a large number of participants (n=576) with moderate-to-severe chronic kidney disease and to implement unique insulin dose adjustment algorithms in this population. Additionally, to our knowledge, this is the first clinical trial in patients with type 2 diabetes and moderate-to-severe chronic kidney disease that has shown clear effects of a GLP-1 receptor agonist on eGFR.

### Implications of all the available evidence

Our findings show that once-weekly dulaglutide, compared with titrated daily insulin glargine, both combined with insulin lispro, attenuated the decline in eGFR in patients type 2 diabetes and moderate-to-severe chronic kidney disease. These benefits were achieved while lowering $HbA_{1c}$ to a similar extent to insulin glargine, but with weight loss and a substantially lower rate of hypoglycaemia.

## Introduction

Diabetic kidney disease occurs in about 40% of patients with type 2 diabetes.[1] Moreover, chronic kidney disease, whether attributable to diabetes or not, considerably increases the complexity and risks of diabetes management.[2] In moderate-to-severe chronic kidney disease, treatment options for hyperglycaemia are limited.[3] Many antihyperglycaemic drugs, including insulin, are primarily cleared by the kidneys, and therefore require dose adjustments or are contraindicated for patients with chronic kidney disease.[4,5] These patients are at an increased risk of hypoglycaemia because of reduced drug clearance and impaired gluconeogenesis by the kidney.[6] Therefore, safe and effective antihyperglycaemic drugs that confer a reduced risk of hypoglycaemia are needed for this population.

Dulaglutide is a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist approved for the treatment of type 2 diabetes.[7] It is composed of two identical GLP-1 (7–37) analogues that are protected against dipeptidyl peptidase-4 (DPP-4) action and fused to a modified IgG4 Fc fragment by a small peptide link.[7] Dulaglutide is not cleared by the kidney and administration to patients with mild-to-severe impairment of kidney function does not increase drug exposure, according to pharmacokinetic findings.[7] Therefore, no dose adjustment for dulaglutide is recommended for patients with chronic kidney disease. The available data suggest that GLP-1 receptor agonists, including dulaglutide, do not have adverse effects on the kidney.[8–11] Furthermore, preclinical evidence suggests that several direct GLP-1 receptor agonist-related mechanisms—including reductions in protein kinase C signalling, oxidative stress, and inflammatory responses—might actually protect the kidney.[12,13] In clinical trials designed to assess cardiovascular safety outcomes for two GLP-1 receptor agonists, liraglutide and semaglutide mitigated macroalbuminuria onset and progression.[14–16] The slope of estimated glomerular filtration rate (eGFR) decline was also attenuated with liraglutide in patients with an eGFR of 30–59 mL/min per 1·73 $m^2$.[16] However, there have been few clinical studies done on GLP-1 receptor agonists in patients with moderate-to-severe chronic kidney disease and most were placebo-controlled.

The aim of the AWARD-7 trial was to assess the glycaemic efficacy and overall safety, including kidney-related safety, of once-weekly dulaglutide compared with daily insulin glargine as basal therapy, both in combination with insulin lispro, for patients with type 2 diabetes and moderate-to-severe chronic kidney disease.

## Methods

### Study design and participants

AWARD-7 was a 52-week, randomised, multicentre, open-label (masked dulaglutide dose), parallel-arm trial done at 99 clinical research sites in nine countries (Brazil, Hungary, Mexico, Poland, Romania, South Africa, Spain, Ukraine, and the USA).

Adults aged 18 years or older with type 2 diabetes and moderate-to-severe chronic kidney disease (stages 3–4)[1] were eligible for inclusion. Key inclusion criteria included the following: $HbA_{1c}$ in the range 7·5–10·5% (58·46–91·25 mmol/mol); treatment with insulin plus an oral antihyperglycaemic drug or only insulin treatment; and treatment with a maximum tolerated dose of either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker. Key exclusion criteria included the following: type 1 diabetes; treatment with oral antihyperglycaemic drug without insulin; treatment with GLP-1 receptor agonists or a DPP-4 inhibitor; and chronic kidney disease stage 5,

maintenance dialysis treatment, likelihood of requiring dialysis or a kidney transplant during the study, or acute kidney injury within 2 months before randomisation. A full list of eligibility criteria is available in the appendix. Enrolment was managed to achieve approximately a 2:1 ratio of participants with chronic kidney disease stages 3 and 4. Patients were enrolled by the clinical research sites and the team responsible for the randomisation process was not involved in any other part of the study.

The trial was done in accordance with the Declaration of Helsinki, the International Ethical Guidelines of the Council for International Organizations of Medical Sciences, and the Good Clinical Practice guidelines of the International Conference on Harmonisation. Local institutional review boards approved the protocol. All participants provided written informed consent.

### Randomisation and masking

Participants were randomly assigned (1:1:1) by use of a computer-generated random sequence with an interactive response system to receive once-weekly dulaglutide 1·5 mg, once-weekly dulaglutide 0·75 mg, or daily titrated insulin glargine, according to a stratification mechanism that accounted for baseline chronic kidney disease severity (stage 3a, 3b, or 4), baseline macroalbuminuria, and geographical region (western USA; eastern USA; Brazil and Mexico; Hungary, Poland, and Spain; Romania, South Africa, and Ukraine). AWARD-7 was an open-label study with respect to assignment to dulaglutide or insulin, but with the investigators and patients masked to the dose of dulaglutide.

### Procedures

The study consisted of three sequential phases: a 3–13 week screening and lead-in period, a 52 week treatment period, and a 4 week safety follow-up period (appendix). The study included 22 study visits during the treatment period (one visit every week for the first month, every 2 weeks until 26 weeks, and 4–6 weeks apart until 52 weeks). For participants who were receiving oral anti-hyperglycaemic drugs before the study, those agents were discontinued in the first week, and pre-study insulin treatment was optimised during a 12 week lead-in period. For participants treated only with insulin before the study, pre-study insulin treatment was optimised during a 3 week lead-in period. All participants discontinued their pre-study insulin regimens at randomisation and were randomly assigned to dulaglutide 1·5 mg, dulaglutide 0·75 mg, or insulin glargine. All participants received titrated mealtime insulin lispro by subcutaneous injection (the dosing algorithm is detailed in the appendix). Study participants assigned to dulaglutide received once-weekly dulaglutide (1·5 mg or 0·75 mg) subcutaneous injections in the skinfold of the left or right abdominal wall. A new prefilled syringe was used for each injection, which was administered at roughly the same time of day each week. Participants assigned to insulin glargine administered the insulin glargine dose daily at bedtime by subcutaneous injection. Dosing adjustment for insulin glargine was made at least weekly, but could be made as frequently as every 3 days on the basis of the mean of the previous three self-monitored fasting blood glucose (FBG) values. Insulin glargine doses (in the glargine group) were titrated to target self-monitored FBG concentrations of 100–150 mg/dL (5·6–8·3 mmol/L) (appendix).

See Online for appendix

All participants were instructed to administer their prandial insulin lispro by subcutaneous injection with the three largest meals of the day. Dosing adjustment for insulin lispro was made at least weekly, but could be made as frequently as every 3 days. The mean of the previous three self-monitored blood glucose values for a given meal were to be used to determine whether an adjustment in dose was needed. If the mean glucose value was within the target range, then there was no change in treatment dose. In all study groups, insulin lispro doses were titrated to target preprandial glucose concentrations of 120–180 mg/dL (6·7–10·0 mmol/L) (appendix). Insulin dose adjustment algorithms were designed to minimise hypoglycaemia (appendix).

Rescue therapy was given in the event of persistent, severe hyperglycaemia, determined by the investigators. Treatment compliance for each visit interval was defined as the patient taking at least 75% of the required doses of the study drug. For the dulaglutide groups, compliance was further defined as not missing more than two consecutive weekly injections. The overall compliance was calculated for each patient at 26 weeks and 52 weeks. This was done by dividing the number of visits in which the patient was compliant by the total number of visits with compliance data for this patient. The overall compliance was used as one of the factors for determining if a patient was eligible for the per-protocol population.

### Outcomes

The primary efficacy outcome was change in $HbA_{1c}$ from baseline to week 26, with a non-inferiority analysis that compared dulaglutide with insulin glargine. Secondary efficacy outcomes at 26 weeks and 52 weeks included $HbA_{1c}$ measurements at 52 weeks, proportions of participants with $HbA_{1c}$ lower than 7% (53 mmol/mol) or 8% (64 mmol/mol), eight-point self-monitored plasma glucose (SMPG) profiles, FBG, mean daily insulin lispro dose, and the proportion of participants with estimated average glucose lower than 154 mg/dL (8·6 mmol/L) from the eight-point SMPG.

Secondary outcomes were change in eGFR (calculated with the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation by serum cystatin C and serum creatinine), urine albumin-to-creatinine ratio (UACR), bodyweight, rate of hypoglycaemia, and allergic reactions. UACR values were only measured at baseline and at 26 weeks and 52 weeks. eGFR values were measured from baseline through 52 weeks.

Adverse events of interest were kidney events, acute pancreatitis, thyroid neoplasms, cardiovascular events, and allergic or hypersensitivity events. These adverse events were prospectively collected by investigators, and other adverse events were self-reported and collected by investigators on electronic case report forms. Additional prespecified secondary measures were changes in serum creatinine, creatinine clearance calculated with the Cockroft Gault equation, and eGFR calculated with the Modification of Diet in Renal Disease study equation (MDRD). The CKD-EPI equation was the primary method for eGFR assessment because it provides a more accurate and precise estimate of GFR.[17]

Death and cardiovascular, pancreatitis, and kidney events were prospectively adjudicated by an independent clinical endpoint committee on the basis of a prespecified adjudication process (adjudication committee members were masked to treatment assignments). Kidney events were defined as any increase in serum creatinine of 30% or greater above baseline, a conservative threshold designed to broadly capture potentially relevant events. End-stage renal disease events were not adjudicated and were summarised as reported by the investigators on the adjudication case report forms or as adverse events. Adjudicated cardiovascular events are described in the appendix. Additional prespecified subgroup analyses were done by baseline UACR.

### Statistical analysis

We calculated that, assuming no difference in change from baseline in $HbA_{1c}$ between dulaglutide 1·5 mg and insulin glargine, a sample size of 564 randomised patients, with 150 completers per group at 26 weeks, would provide 88% power to show non-inferiority of dulaglutide 1·5 mg to insulin glargine at the two-sided significance level of 0·05, with a non-inferiority margin of 0·4% and an SD of 1·1%. Tests of treatment effects were done at a two-sided α level of 0·05 and two-sided 95% CIs are reported, unless otherwise indicated.

The primary objective was to show that the effect of treatment with once-weekly dulaglutide on $HbA_{1c}$ change from baseline to 26 weeks was non-inferior to insulin glargine. Sequential gatekeeping was only implemented for multiple testing for the $HbA_{1c}$ analyses at 26 weeks, using the following hierarchical sequence: non-inferiority of dulaglutide 1·5 mg versus insulin glargine with a margin of 0·4%; non-inferiority of dulaglutide 0·75 mg versus insulin glargine with a margin of 0·4%; non-inferiority of dulaglutide 1·5 mg with a margin of 0·3%; superiority of dulaglutide 1·5 mg over insulin glargine; non-inferiority of dulaglutide 0·75 mg with a margin of 0·3%; and superiority of dulaglutide 0·75 mg over insulin glargine (appendix). The p values were not adjusted for multiplicity for secondary objectives.

The primary objective was assessed by use of a mixed-effects repeated measures model that included treatment, stratification factors, chronic kidney disease stage, visit, treatment-by-visit interaction, baseline $HbA_{1c}$, and log of the baseline eGFR (within chronic kidney disease stages) as fixed, explanatory variables and participant as a random effect. The primary analysis and all glycaemic efficacy variable analyses were based on the modified intention-to-treat population, defined as all randomly assigned patients who received at least one dose of study treatment (dulaglutide or insulin glargine) and had at least one post-randomisation $HbA_{1c}$ measurement.

Statistical analyses of adverse events were done for treatment-emergent adverse events, discontinuation due to adverse event or death, serious adverse events, and other notable adverse events of interest. For categorical measures, summary statistics included sample size, frequency, and percentages. Unless otherwise specified, a Cochran-Mantel-Haenszel test, adjusted for chronic kidney disease severity (stages 3a, 3b, or 4), was used for the treatment comparisons. All adverse events occurring after the patient received the first trial dose were required to be reported. Data obtained after rescue (ie, use of additional antihyperglycaemic rescue therapy for severe, persistent hyperglycaemia) or discontinuation of study treatment were not included in efficacy or hypoglycaemia analyses; these data could have biased glycaemic results because these participants received other antihyperglycaemic drugs. However, data from these patients were included up to the point of receiving other antihyperglycaemic drugs or study treatment discontinuation. No missing data were imputed (except in a prespecified sensitivity analysis of the primary endpoint that used last observation carried forward). Analyses for the per-protocol population and additional sensitivity and supportive analyses were done for the primary outcome as described in the appendix. All analyses done were prespecified in the protocol.

The safety population was used in the analyses of all safety measures and measures of kidney function and bodyweight. The safety population was defined as all participants who received at least one dose of randomly assigned treatment (dulaglutide or insulin glargine) and had any post-dose data. Mixed-effects repeated measures model analyses similar to those done for the $HbA_{1c}$ analyses were done for eGFR and UACR. Because of expected skewness, these analyses were prespecified to be done on a log scale and estimates from these models were back-transformed and presented as geometric least squares mean (LSM) for eGFR or percentage change from baseline for UACR, with inclusion of baseline values and systolic blood pressure as covariates. Change from baseline in untransformed eGFR was also computed. Data are presented as LSM and SE or 95% CI.

Statistical analyses were done with SAS software version 9.1 or higher. Unless otherwise specified, p values lower than 0·05 were regarded as significant. Additional details of data analyses are described in the appendix. This study is registered with ClinicalTrials.gov, number NCT01621178.

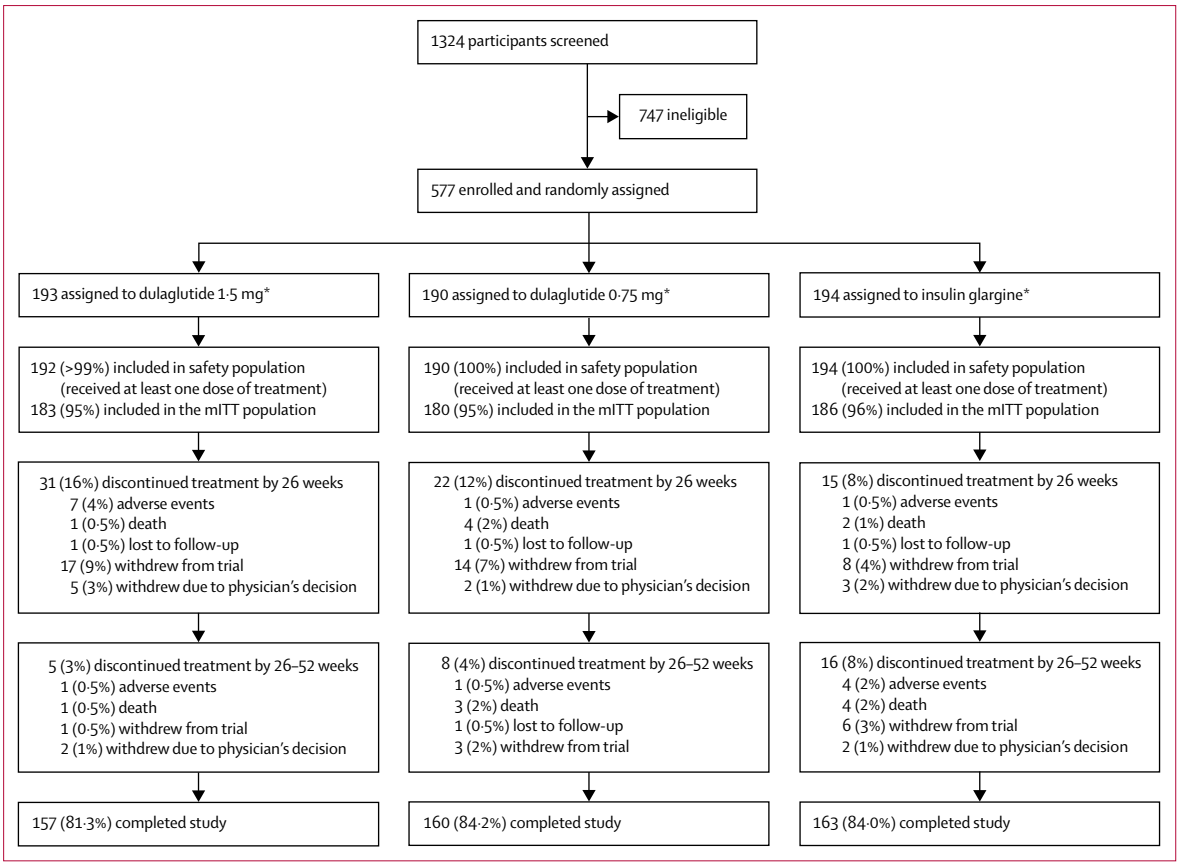


***Figure 1:*** **Trial profile**
mITT=modified intention-to-treat. *Participants who required glycaemic rescue for severe, persistent hyperglycaemia up to week 26: dulaglutide 1·5 mg, 11 (5·7%) of 192; dulaglutide 0·75 mg, ten (5·3%) of 190; insulin glargine, one (0·5%) of 194; up to week 52: dulaglutide 1·5 mg, 12 (6·2%) of 192; dulaglutide 0·75 mg, ten (5·3%) of 190; insulin glargine, three (1·5%) of 194.

### Role of the funding source

The funder of this study was involved in the study design, data collection, data review, data analysis, and drafting of the report. All authors had full access to all the data relevant to this report and shared final responsibility for the decision to submit for publication.

## Results

Enrolment began on Aug 15, 2012, and ended on Nov 30, 2015; the last patient completed the study on Dec 20, 2016. Overall, 577 participants were randomly assigned to study treatment (figure 1), and 480 participants completed 52 weeks of treatment. Most study discontinuations were due to participant decision or adverse events. Baseline demographics, clinical characteristics, and concomitant medication use were similar between groups (table 1; appendix).

At 26 weeks, all treatment groups had mean decreases in $HbA_{1c}$ from baseline that were significant within each group (LSM –1·2%, SE 0·1 [–13·0 mmol/mol, 1·4] with dulaglutide 1·5 mg; –1·1%, 0·1 [–12·2 mmol/mol, 1·3] with dulaglutide 0·75 mg; –1·1%, 0·1 [–12·4 mmol/mol, 1·3] with insulin glargine; all p<0·0001; figure 2A; appendix). Both dulaglutide doses were non-inferior to insulin glargine, with a 0·4% (4·4 mmol/mol) non-inferiority margin (one-sided p≤0·0001, both comparisons). Treatment with dulaglutide 1·5 mg achieved noninferiority at the 0.3% margin but not superiority; therefore, hierarchy testing ended. Reductions in $HbA_{1c}$ were sustained over 52 weeks (figure 2A; appendix). Results of the per-protocol population analysis were consistent with those of the primary analysis in the modified intention-to-treat population (non-inferiority was achieved for both dulaglutide doses; appendix). Results of additional sensitivity analysis, including all data obtained after receiving rescue treatment or study treatment discontinuation, and other supportive analyses (appendix) were consistent with this prespecified mixed-effects repeated measures model primary analysis in the modified intention-to-treat population (data not shown). The proportions of participants achieving $HbA_{1c}$ targets of lower than 8% and lower than 7% were similar between groups at both 26 and 52 weeks (69–78% of participants reaching lower than 8% and 29–38% reaching lower than 7%; appendix).

| | Dulaglutide 1·5 mg (n=192) | Dulaglutide 0·75 mg (n=190) | Insulin glargine (n=194) |
|---|---|---|---|
| Sex (women, men) | 88 (46%), 104 (54%) | 86 (45%), 104 (55%) | 101 (52%), 93 (48%) |
| Age (years) | 64·7 (8·8) | 64·7 (8·6) | 64·3 (8·4) |
| Duration of diabetes (years) | 17·6 (8·7) | 18·0 (8·8) | 18·7 (8·7) |
| Race or ethnic origin | | | |
| Hispanic or Latino | 78 (41%) | 75 (39%) | 79 (41%) |
| Native American or Alaskan Native | 12 (6%) | 17 (9%) | 18 (9%) |
| Asian | 7 (4%) | 4 (2%) | 5 (3%) |
| Black or African American | 26 (14%) | 36 (19%) | 26 (14%) |
| Native Hawaiian or other Pacific Islander | 0 (0%) | 0 (0%) | 1 (1%) |
| White | 134 (71%) | 122 (66%) | 137 (71%) |
| Multiple | 10 (5%) | 7 (4%) | 6 (3%) |
| $HbA_{1c}$ (%) | 8·6 (0·9) | 8·6 (1·1) | 8·6 (1·0) |
| $HBA_{1c}$ (mmol/mol [SE]) | 70·5 (9·3) | 70·3 (12·0) | 70·1 (10·6) |
| $HbA_{1c}$ >8·5% | 96 (50%) | 91 (48%) | 81 (42%) |
| Weight (kg) | 88·1 (16·0) | 90·9 (18·3) | 88·2 (18·5) |
| BMI ($kg/m^2$) | 32·1 (4·8) | 33·0 (5·5) | 32·4 (5·3) |
| Sitting systolic blood pressure (mm Hg) | 136·8 (13·7) | 137·4 (14·9) | 136·7 (14·3) |
| Sitting diastolic blood pressure (mm Hg) | 75·1 (9·1) | 74·6 (9·5) | 74·1 (9·0) |
| Total daily insulin dose (U/day) | 58·8 (30·1) | 56·6 (31·2) | 59·3 (34·2) |
| Duration of chronic kidney disease* (years) | 4·2 (5·6) | 4·0 (4·9) | 3·5 (4·0) |
| eGFR by creatinine ($mL/min$ per 1·73 $m^2$) | 38·1 (13·2) | 38·3 (12·3) | 38·5 (13·0) |
| eGFR by creatinine ($mL/min$ per 1·73 $m^2$, geometric mean [SE]) | 35·7 (1·0) | 36·2 (0·9) | 36·1 (0·9) |
| Baseline eGFR ≥60 to <90 | 9 (5%) | 7 (4%) | 14 (7%) |
| Baseline eGFR ≥45 to <60 | 53 (28%) | 53 (28%) | 51 (26%) |
| Baseline eGFR ≥30 to <45 | 73 (38%) | 75 (39%) | 67 (35%) |
| Baseline eGFR ≥15 to <30 | 55 (29%) | 55 (29%) | 61 (31%) |
| Baseline eGFR <15 | 2 (1%) | 0 (0%) | 1 (1%) |
| eGFR by cystatin C ($mL/min$ per 1·73$m^2$, mean [SE]) | 37·3 (14·2) | 37·7 (13·7) | 38·3 (14·8) |
| eGFR by cystatin C ($mL/min$ per 1·73$m^2$, geometric mean [SE]) | 34·8 (1·0) | 35·4 (0·9) | 35·6 (1·0) |
| UACR (mg/g, median [IQR]) | 213·7 (45·8–868·0) | 233·6 (36·7–946·5) | 195·6 (30·1–1015·1) |
| Normal albuminuria (UACR <30) | 34 (18%) | 44 (23%) | 48 (25%) |
| Microalbuminuria (UACR 30–300) | 74 (39%) | 61 (32%) | 56 (29%) |
| Macroalbuminuria (UACR >300) | 84 (44%) | 84 (44%) | 90 (46%) |
| Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use (mITT population) | 165 (90%) | 170 (94%) | 174 (94%) |

Data are mean (SD) or n (%), unless otherwise noted. Race and ethnic origins were self-reported. If baseline information was missing for some patients, the number of patients used in the denominator for percentage calculation was smaller than the total number of patients for the treatment group. Estimated glomerular filtration rate (eGFR) was calculated based on the Chronic Kidney Disease Epidemiology Collaboration equation based on serum creatinine or serum cystatin C.[17,18] UACR=urine albumin-to-creatinine ratio. *Chronic kidney disease stage 3 or higher at baseline. Concomitant antihypertensive use represents the modified intention-to-treat (mITT) population, therefore the denominators for percentage calculation are: 183 for dulaglutide 1·5 mg, 180 for dulaglutide 0·75 mg, and 186 for insulin glargine.

***Table 1:*** **Baseline characteristics**

FBG increased from baseline with both dulaglutide doses at 26 weeks and 52 weeks and decreased with insulin glargine at 26 weeks, with significant differences between the dulaglutide and insulin groups at both timepoints (figure 2B; appendix). However, greater reductions of postprandial glycaemic excursions were observed with both doses of dulaglutide in the eight-point SMPG profiles (appendix). Bodyweight decreased with both dulaglutide doses and increased with insulin glargine at 26 weeks and 52 weeks (figure 2C; appendix).

In the insulin glargine group, mean daily doses of insulin glargine increased from baseline and stabilised by 12 weeks (appendix). The insulin glargine dose adjustment algorithm targeted self-monitored FBG between 100 mg/dL and 150 mg/dL (5·6–8·3 mmol/L) to minimise hypoglycaemia risk in the moderate-to-severe chronic kidney disease population. At week 52, the proportion of study participants meeting the self-monitored FBG target of 150 mg/dL [8·3 mmol/L] or lower, on the basis of the insulin dose adjustment algorithm, was 138 (80%) of 172 in the insulin glargine group.

Daily insulin lispro doses at baseline were similar across treatment groups. In all groups, mean daily

insulin lispro doses increased progressively from baseline to roughly 26 weeks and were generally stable from 26 to 52 weeks. Increases in mean insulin lispro doses were greater with dulaglutide 0·75 mg than with insulin glargine or dulaglutide 1·5 mg (appendix).

Baseline eGFR (geometric mean) was 35·3 (SD 0·6) mL/min per 1·73 m² with CKD-EPI cystatin C and 36·0 (0·5) mL/min per 1·73 m² with CKD-EPI creatinine. At 26 weeks and 52 weeks, with both methods, eGFR did not change with either dulaglutide dose, but declined from baseline with insulin glargine (figure 3 and appendix). At 52 weeks, eGFR was significantly higher with both dulaglutide doses than with insulin glargine when calculated with use of serum cystatin C, and significantly higher with dulaglutide 1·5 mg than with insulin glargine when calculated with use of serum creatinine. Overall, the decline in eGFR change was significantly smaller for both dulaglutide doses compared with insulin glargine. Additionally, eGFR measures collected 4 weeks after treatment discontinuation were consistent with the last observed eGFR measures during treatment, although these data were not statistically analysed (appendix). Changes in serum creatinine, eGFR (with MDRD equation), and creatinine clearance were also consistent with the CKD-EPI eGFR measures (appendix).

In participants with baseline macroalbuminuria (UACR >300 mg/g), the decline in eGFR (CKD-EPI cystatin C) was significantly smaller with both dulaglutide doses than with insulin glargine at both 26 and 52 weeks (figure 4; appendix). In participants without baseline macroalbuminuria, the decline in eGFR (CKD-EPI cystatin C) was smaller with dulaglutide 1·5 mg than with insulin glargine at 26 weeks (figures 4A–B; appendix); at 52 weeks, no significant differences were observed.

Decreases from baseline in UACR were significant within each group at 26 weeks and within both dulaglutide groups at 52 weeks, but did not differ significantly between groups at both 26 weeks (LSM: insulin glargine, –16·4% [95% CI –29·0 to –1·5]; dulaglutide 1·5 mg, –27·7% [–38·7 to –14·8], p=0·167 *vs* insulin glargine; dulaglutide 0·75 mg, –26·7% [–37·9 to –13·5], p=0·211 *vs* insulin glargine) and 52 weeks (LSM: insulin glargine, –13·0% [95% CI –27·1 to 3·9]; dulaglutide 1·5 mg, –22·5% [–35·1 to –7·5], p=0·317 *vs* insulin glargine; dulaglutide

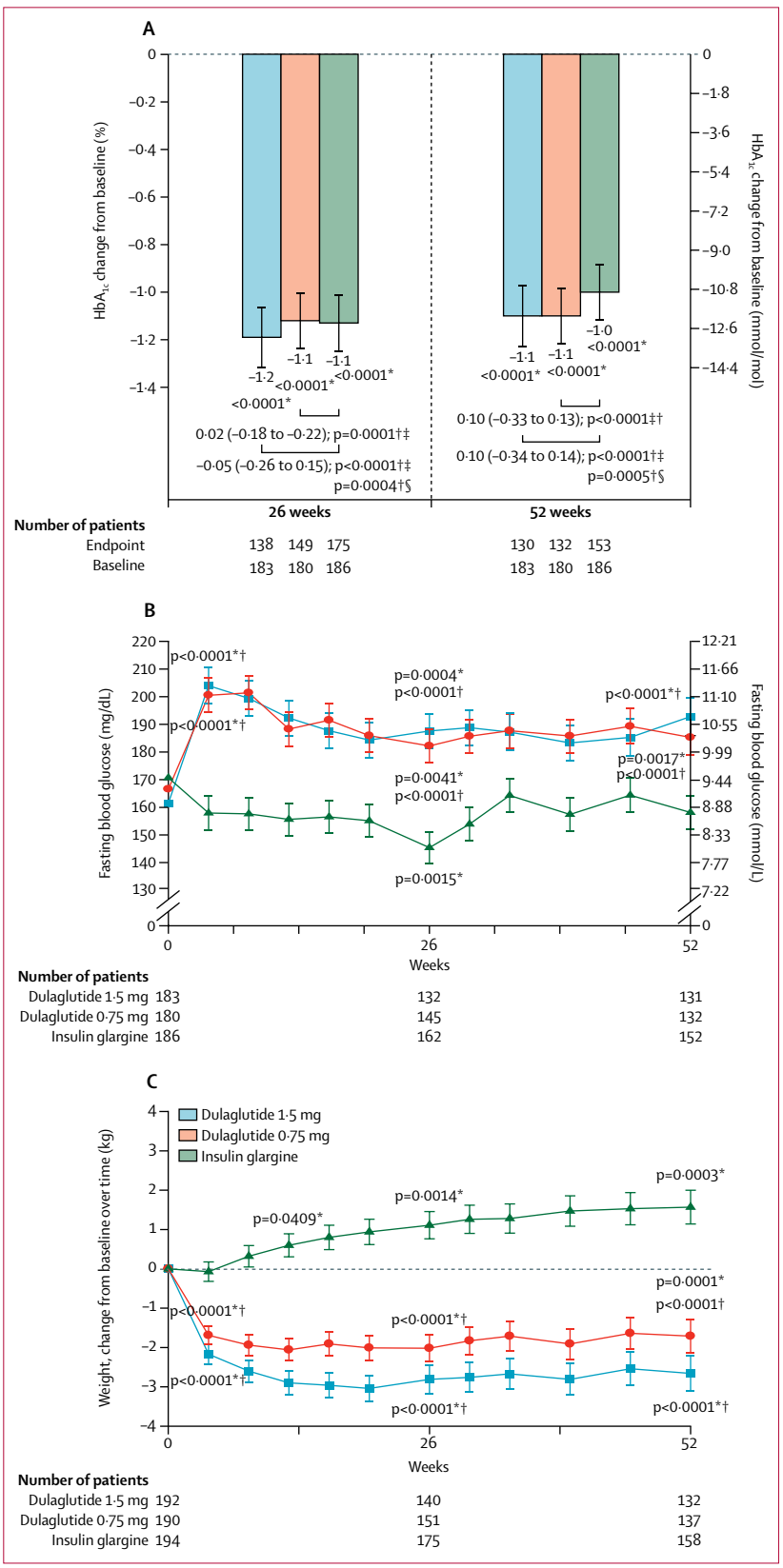


***Figure 2:*** **Measures of glycaemic control and bodyweight**
(A) Change from baseline in $HbA_{1c}$ at week 26 and week 52; estimated least squares mean (LSM) and treatment differences (95% CI) are shown. (B) Fasting blood glucose over time. (C) Change from baseline in bodyweight over time. Data are presented as LSM (SE) unless otherwise noted, from modified intention-to-treat population (or safety population for change in bodyweight over time), excluding data after rescue or study drug discontinuation. Numbers of patients analysed at baseline and endpoints are shown under the x axis. p values are reported for statistical significance at first occurrence and at the 26 and 52 week prespecified analyses points. *Versus baseline. †Versus insulin glargine. ‡0·4% non-inferiority margin versus insulin glargine. §0·3% non-inferiority margin versus insulin glargine.

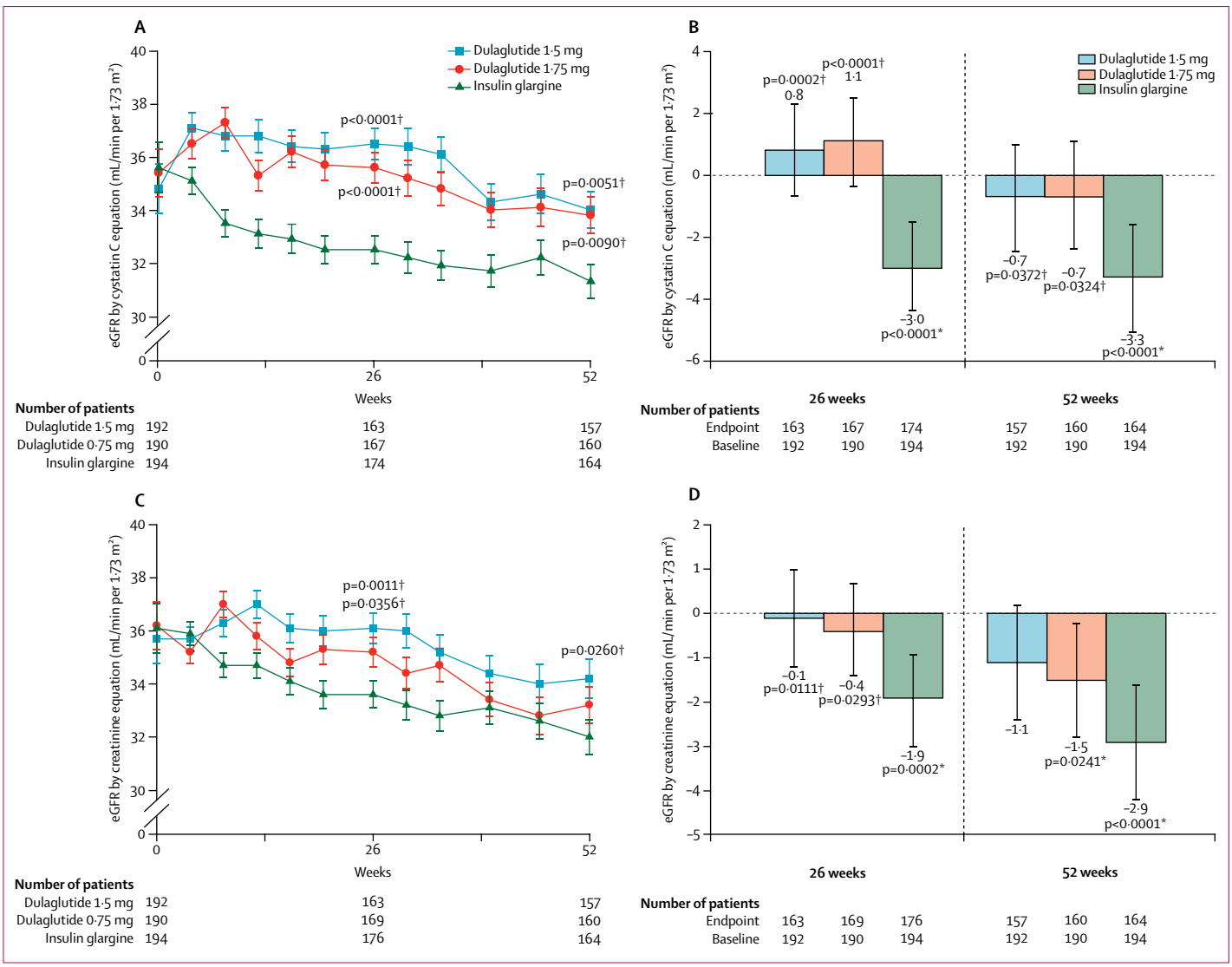


***Figure 3:*** **Change in estimated glomerular filtration rate**

Values estimated by Chronic Kidney Disease Epidemiology Collaboration equation by cystatin C or creatinine. (A and C) Data presented as estimated glomerular filtration rate (eGFR) values by geometric least squares mean (LSM, SE) from log-transformed analysis; statistical significance was only tested for between-group differences versus insulin glargine. (B and D) Data presented as actual untransformed change from baseline in eGFR values (LSM, 95% CI); p values are reported for statistical significance versus baseline (within group) and versus insulin glargine. Values shown above or below the bars are LSM. Numbers of patients analysed at baseline and endpoints are shown under the x axis. Data are for safety population by use of a mixed-effects repeated measures model analysis. p values are reported for statistical significance at the 26 and 52 week prespecified analyses points. *Versus baseline. †Versus insulin glargine.

0·75 mg, –20·1% [–33·1 to –4·6], p=0·458 *vs* insulin glargine). Notably, in participants with baseline macroalbuminuria (UACR >300 mg/g), UACR decreased from baseline in a dose-related manner in the dulaglutide groups at 26 weeks and 52 weeks (figure 4C). At both timepoints, UACR decreases were significantly larger with dulaglutide 1·5 mg than with insulin glargine (LSM at 26 weeks: insulin glargine, –14·3% [95% CI –30·9 to 6·3]; dulaglutide 1·5 mg, –43·1% [–54·7 to –28·6; p=0·008 *vs* insulin glargine]; dulaglutide 0·75 mg, –25·3% [–40·2 to –6·8; p=0·360 *vs* insulin glargine]; LSM at 52 weeks: insulin glargine, 0·1% [95% CI –18·8 to 23·4]; dulaglutide 1·5 mg, –29·0% [–43·0 to –11·5; p=0·020 *vs* insulin glargine]; dulaglutide 0·75 mg, –12·3% [–29·0 to 8·5; p=0·363 *vs* insulin glargine]). Decreases in UACR were not significant with dulaglutide 0·75 mg compared with insulin glargine.

Numerically, but not significantly, smaller proportions of participants treated with dulaglutide had adjudicated kidney events resulting in chronic kidney disease progression by 52 weeks (19 [10%] of 192 with dulaglutide 1·5 mg, p=0·075 *vs* insulin glargine; 24 [13%] of 190 with dulaglutide 0·75 mg, p=0·349 *vs* insulin glargine; 31 [16%] of 194 with insulin glargine; appendix). End-stage renal disease occurred in 38 participants by 52 weeks, without significant between-group differences

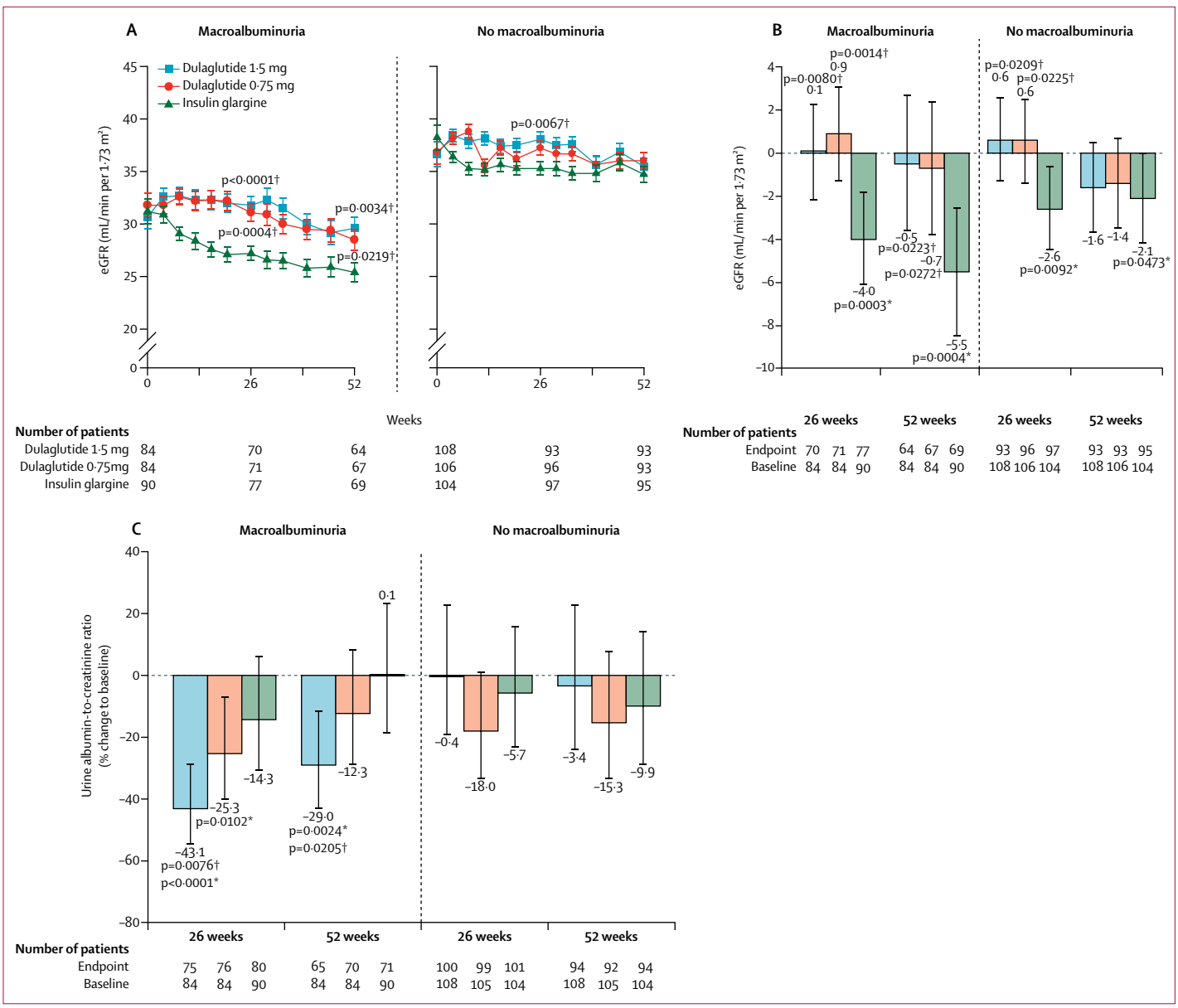


***Figure 4:*** **Changes in estimated glomerular filtration rate and albuminuria by macroalbuminuria status at baseline**
(A) Estimated glomerular filtration rate (eGFR; calculated by Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation by cystatin C) by macroalbuminuria status at baseline, presented as geometric least squares mean (LSM, SE) from log-transformed analysis; statistical significance was only tested for between-group differences versus insulin glargine. (B) Actual untransformed change from baseline in eGFR (calculated by CDK-EPI equation by cystatin C) by macroalbuminuria status at baseline, with values presented as LSM (95% CI), with p values reported for statistical significance versus baseline (within group) and versus insulin glargine; values shown above or below the bars are LSM. (C) Urine albumin-to-creatinine ratio (UACR) by macroalbuminuria status at baseline, presented as LSM (95% CI) for percentage change from baseline, with p values reported for statistical significance versus baseline (within group) and versus insulin glargine. Data presented for safety population, by use of a mixed-effects repeated measures model analysis. p values are reported for statistical significance at the 26 and 52 week prespecified analyses points. Numbers of patients analysed at baseline and endpoints are shown under the x axis. *Versus baseline. †Versus insulin glargine.

(eight [4%] of 192 with dulaglutide 1·5 mg, 14 [7%] of 190 with dulaglutide 0·75 mg, 16 [8%] of 194 with insulin glargine; overall p=0·231; table 2).

The overall proportion of patients with serious adverse events did not differ between groups (table 2). The most commonly reported serious adverse events were hypoglycaemia (20 [4%] of 576 serious adverse events), acute myocardial infarction (nine [2%] of 576), acute kidney injury (nine [2%] of 576), and increase in blood creatinine concentrations (eight [1%] of 576). No significant differences were observed between groups for these serious adverse events, apart from lower rates of hypoglycaemia with dulaglutide 1·5 mg treatment compared with insulin glargine.

Higher rates of nausea and diarrhoea were observed with both dulaglutide doses than with insulin glargine

| | Dulaglutide 1·5 mg (n=192) | Dulaglutide 0·75 mg (n=190) | Insulin glargine (n=194) | Dulaglutide 1·5 mg *vs* insulin glargine p value | Dulaglutide 0·75 mg *vs* insulin glargine p value | Overall p value |
|---|---|---|---|---|---|---|
| All deaths during treatment period (52 weeks) | 2 (1%) | 7 (4%) | 6 (3%) | .. | .. | .. |
| Serious adverse events (52 weeks) | 38 (20%) | 45 (24%) | 52 (27%) | 0·113 | 0·516 | 0·279 |
| Treatment-emergent adverse events (≥1 event; 52 weeks) | 172 (90%)* | 168 (88%) | 158 (81%) | 0·022 | 0·059 | 0·039 |
| Treatment-emergent adverse events (≥5% of patients; 52 weeks) | | | | | | |
| Blood creatinine increased | 73 (38%) | 71 (37%) | 88 (45%) | 0·154 | 0·119 | 0·219 |
| Diarrhoea | 33 (17%)* | 30 (16%)* | 14 (7%) | 0·003 | 0·011 | 0·008 |
| Nausea | 38 (20%)† | 27 (14%)* | 9 (5%) | <0·0001 | 0·001 | <0·0001 |
| Glomerular filtration rate decreased | 15 (8%) | 20 (11%) | 25 (13%) | 0·113 | 0·606 | 0·279 |
| Vomiting | 26 (14%)* | 16 (8%) | 9 (5%) | 0·002 | 0·108 | 0·007 |
| Hypertension | 14 (7%) | 13 (7%) | 21 (11%) | 0·228 | 0·182 | 0·318 |
| Urinary tract infection | 14 (7%) | 12 (6%) | 21 (11%) | 0·228 | 0·099 | 0·223 |
| Upper respiratory tract infection | 8 (4%)* | 13 (7%) | 19 (10%) | 0·032 | 0·292 | 0·097 |
| Oedema, peripheral | 11 (6%) | 12 (6%) | 15 (8%) | 0·423 | 0·565 | 0·709 |
| Influenza | 12 (6%) | 15 (8%) | 10 (5%) | 0·603 | 0·264 | 0·511 |
| Hyperkalaemia | 12 (6%) | 8 (4%) | 13 (7%) | 0·900 | 0·287 | 0·543 |
| Nasopharyngitis | 11 (6%) | 9 (5%) | 12 (6%) | 0·822 | 0·517 | 0·804 |
| Weight increased | 8 (4%) | 8 (4%) | 16 (8%) | 0·098 | 0·084 | 0·126 |
| Dizziness | 8 (4%) | 11 (6%) | 10 (5%) | 0·651 | 0·810 | 0·767 |
| Constipation | 12 (6%) | 10 (5%) | 6 (3%) | 0·128 | 0·286 | 0·315 |
| Cough | 7 (4%) | 7 (4%) | 14 (7%) | 0·105 | 0·115 | 0·147 |
| Hypoglycaemia | 3 (2%)* | 9 (5%) | 16 (8%) | 0·002 | 0·159 | 0·010 |
| Adverse events of special interest (safety follow-up period) | | | | | | |
| Adjudicated kidney events | 79 (41%) | 73 (38%) | 91 (47%) | 0·254 | 0·093 | 0·397 |
| Adjudicated pancreatitis | 2 (1%) | 0 (0%) | 1 (1%) | .. | .. | .. |
| Adjudicated death or cardiovascular event | 10 (5%) | 18 (9%) | 13 (7%) | .. | .. | .. |
| All death | 3 (2%) | 9 (5%) | 6 (3%) | .. | .. | .. |
| Cardiovascular death | 2 (1%) | 6 (3%) | 4 (2%) | .. | .. | .. |
| Transition to end-stage renal disease | | | | | | |
| Transition to maintenance dialysis‡ | 0 (0%) | 2 (1%) | 2 (1%) | .. | .. | 0·477 |
| Kidney transplantation§ | 0 (0%) | 0 (0%) | 0 (0%) | .. | .. | .. |
| Without reported dialysis or transplant¶ | 8 (4%) | 12 (7%) | 14 (7%) | .. | .. | 0·430 |
| Total | 8 (4%) | 14 (8%) | 16 (8%) | .. | .. | 0·231 |
| Death due to kidney diseases (confirmed by adjudication) | 0 (0%) | 0 (0%) | 0 (0%) | | | |
| Study treatment or study discontinuation due to death or adverse event | 24 (13%) | 19 (10%) | 12 (6%) | 0·025 | 0·130 | 0·082 |
| Study discontinuation due to death or adverse event | 10 (5%) | 9 (5%) | 11 (6%) | 0·901 | 0·755 | 0·947 |

Data presented as n (%). The safety follow-up period included the 4 weeks after the treatment period. If baseline information was missing for some patients, the number of patients used in the denominator for percentage calculation was smaller than the total number of patients for the treatment group. Some patients did not have both baseline and at least one post-baseline data; therefore, the denominators can differ. *p<0·05 versus insulin glargine. †p<0·0001 versus insulin glargine. ‡Patients with chronic dialysis reported by investigator on renal endpoint form or with a dialysis adverse event (searched on the Medical Dictionary for Regulatory Activities [MedDRA] with the preferred terms "dialysis", "dialysis device insertion", "haemodialysis", "haemofiltration", "peritoneal dialysis", "continuous haemodiafiltration", or "artificial kidney device user"). §Patients with renal transplant reported by investigator on renal endpoint form or with renal transplant adverse event (searched on MedDRA with the preferred terms "renal and liver transplant", "renal and pancreas transplant", "renal replacement therapy", or "renal transplant"). ¶Patients with end-stage renal disease without dialysis or transplant reported by investigator on renal endpoint form or with end-stage renal disease adverse event (searched on MedDRA with the preferred terms "diabetic end stage renal disease", "renal failure", or "end stage renal disease").

***Table 2:*** **Adverse events**

(table 2); vomiting was most common with dulaglutide 1·5 mg. The number of study or treatment discontinuations due to adverse events was higher with dulaglutide 1·5 mg than with insulin glargine. Most adverse events leading to study or treatment discontinuations with dulaglutide were gastrointestinal events (dulaglutide 1·5 mg 13 [7%] of 192; dulaglutide 0·75 mg four [2%] of 190; insulin glargine, none [0%] of 194).

The rates and proportions of total, documented symptomatic, and nocturnal hypoglycaemic events (defined as plasma glucose concentration ≤70 mg/dL [3·9 mmol/L]) with dulaglutide were significantly lower than with insulin glargine (appendix). The proportion of patients with severe hypoglycaemia events was lower with dulaglutide 1·5 mg than with insulin glargine (insulin glargine, 13 [7%] of 194; dulaglutide 1·5 mg,

none [0%] of 192 [p=0·0003 *vs* insulin glargine]; dulaglutide 0·75 mg, five [3%] of 190 [p=0·062 *vs* insulin glargine]).

The incidence of adverse events for kidney disease did not differ by group. The majority of these events (ie, an increase in serum creatinine of 30% or greater from baseline during the study) were transient and most events recovered, as defined by serum creatinine values returning to within 10% of baseline (appendix).

Changes in systolic blood pressure did not significantly differ between treatments at any timepoint, apart from a small transient decrease at week 12 with dulaglutide 1·5 mg (LSM –2·3, SE 1·5 mm Hg; p=0·0227) and 0·75 mg (–2·8, 1·5 mm Hg; p=0·0106), compared with insulin glargine (1·2, 1·5 mm Hg; appendix). Changes in diastolic blood pressure did not significantly differ between treatments at any timepoint, apart from a small decrease at week 52 with insulin glargine compared with dulaglutide 1·5 mg (p=0·028) and 0·75 mg (p=0·020; appendix). Both doses of dulaglutide treatment increased heart rate compared with insulin glargine by week four (appendix). Testing for pancreatic and thyroid status, antidrug antibodies, injection site reactions, and vital signs did not detect untoward or unexpected safety signals (appendix).

## Discussion

In participants with type 2 diabetes and moderate-to-severe chronic kidney disease, once-weekly treatment with dulaglutide produced clinically meaningful improvements in glycaemic control, with efficacy similar to that of daily insulin glargine as basal therapy in terms of change in $HbA_{1c}$. Analysis of secondary endpoints suggested that dulaglutide treatment was associated with weight loss, a lower rate of hypoglycaemia, a smaller decline in eGFR, and a greater reduction in albuminuria compared with insulin glargine.

The modified intention-to-treat population was used as the primary efficacy population to assess the effects of treatment regardless of treatment adherence or having significant protocol deviation. A similar degree of glycaemic control, as assessed by change in $HbA_{1c}$, was achieved across study groups. However, once-weekly dulaglutide treatment produced increased reductions in postprandial glucose excursions, while daily basal therapy with insulin glargine led to reduced FBG concentrations. The difference in FBG observed between the dulaglutide and insulin glargine groups is probably related to the study design. The protocol specified that participants were to discontinue their pre-study insulin treatment at randomisation. Participants assigned to insulin glargine had dose titration based on self-monitored FBG, while participants on the dulaglutide group did not. Stopping pre-study insulin treatment at randomisation might have contributed to the increase in FBG observed with dulaglutide. However, patients assigned to insulin glargine had a decrease in FBG due to adjustment of insulin glargine doses. Moreover, once-weekly dulaglutide treatment produced lower rates of hypoglycaemia than did insulin glargine treatment (about 50% lower), despite achieving similar glycaemic control. A reduced risk of hypoglycaemia is a clear safety advantage of GLP-1 receptor agonists[19,20] for patients with moderate-to-severe chronic kidney disease. Implementation of carefully constructed preprandial insulin dosing algorithms, along with consistent self-monitoring of blood glucose, was another important strategy for managing the risk of hypoglycaemia. Notably, the rate of hypoglycaemia with basal insulin glargine treatment was similar to, or lower than, rates reported in studies of patients with diabetes without kidney disease,[19,20] indicating that the overall algorithms used in this study were appropriate for patients with moderate-to-severe chronic kidney disease.

Dulaglutide treatment was associated with a significantly smaller decline in eGFR compared with insulin glargine over 52 weeks. These data suggest that dulaglutide could have specific therapeutic benefits that might slow progression of moderate-to-severe chronic kidney disease in type 2 diabetes. The association between dulaglutide treatment and reduced eGFR decline was most evident in participants with macroalbuminuria. In this subgroup, the mean eGFR decline with dulaglutide 1·5 mg was only about 10% of what was observed with insulin glargine. Although the magnitude of eGFR preservation by dulaglutide treatment seems small in the short term, it might be clinically relevant in the long term if the time period before kidney replacement therapy can be extended. Albuminuria decreased in all treatment groups, but once-weekly dulaglutide led to a substantially greater decrease in UACR than did daily insulin glargine in participants with baseline macroalbuminuria. This UACR effect was dose-related. These benefits were observed despite background treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in more than 90% of participants.

Clinical trials[14–16,21,22] designed to assess cardiovascular safety of GLP-1 receptor agonists and sodium-glucose co-transporter-2 (SGLT2) inhibitors in type 2 diabetes showed a reduced risk of macroalbuminuria and reduced eGFR decline. However, there were significant differences in glycaemic control or blood pressure between groups in those studies. AWARD-7 was unique in that there were no overall between-group treatment differences for glycaemia, blood pressure, or use of renin-angiotensin system inhibitors. Therefore, additional protective mechanisms independent from glycaemic control or blood pressure are likely to be involved in the beneficial effects of dulaglutide. Whereas SGLT2 inhibitors might be beneficial for the kidneys because they reduce glomerular hyperfiltration and restore tubuloglomerular feedback,[21] the possible kidney protective mechanisms of GLP-1 receptor agonists are less clear. Preclinical and human data suggest that GLP-1 receptors are present on glomerular, tubular, and vascular cells in the kidney.[23] The

mechanisms of GLP-1-mediated kidney protection might include anti-inflammatory effects, amelioration of oxidative stress, and vascular endothelium protection.[13,23–26] In mouse models of diabetes, GLP-1 receptor agonist treatment reduced seminal features of diabetic kidney disease (including mesangial expansion and glomerular basement membrane thickening), restored podocyte numbers, and reduced albuminuria. Conversely, these disease features were exacerbated by knocking out the GLP-1 receptor.[24] Additionally, evidence from human studies suggests that GLP-1 might modulate kidney haemodynamics[27] and cause natriuresis,[28] possibly through inhibition of sodium–hydrogen exchange in the proximal tubule.[29]

The overall rate of adverse events related to kidney disease did not differ between randomised groups in AWARD-7. Nearly two-thirds of these events were adjudicated with an outcome of recovery. Similar numbers of participants in each group had adverse events adjudicated with volume depletion as a cause. Notably, numerically, but not significantly, fewer participants treated with dulaglutide had an outcome of chronic kidney disease progression or end-stage renal disease compared with participants treated with insulin glargine. In general, the dulaglutide-associated adverse events were consistent with clinical trials of dulaglutide treatment in participants with diabetes without kidney disease.[7]

Limitations of this study include the open-label design of the trial. Masking treatment allocation was not feasible because of the dose adjustment requirements in the insulin glargine group. Although dulaglutide treatment was associated with a reduced decline in eGFR, the study was not designed to assess clinical endpoints because of the short 1-year treatment duration. Differences in rates of chronic kidney disease progression or end-stage renal disease will require long-term studies to substantiate that the eGFR benefit of dulaglutide treatment translates to reduced rates of these events. Strengths of this study include the active-comparator design, enrolment of substantial numbers of patients with chronic kidney disease stage 4, and assessment of eGFR by both cystatin C-based and creatinine-based equations. Changes in bodyweight could bias eGFR calculations by creatinine-based equations if associated with muscle mass changes. However, eGFR results from the cystatin C-based equation were consistent with those from the creatinine-based equation, indicating that changes in muscle mass are unlikely to explain the eGFR differences between dulaglutide and insulin glargine groups.

In conclusion, the results of AWARD-7 show that once-weekly dulaglutide treatment has similar glycaemic efficacy to daily insulin glargine treatment as basal therapy for patients with type 2 diabetes and moderate-to-severe chronic kidney disease who had not previously attained glycaemic targets with insulin alone or with insulin plus oral antihyperglycaemic regimens. Dulaglutide treatment showed an overall favourable safety profile along with possible therapeutic benefits, including lower rates of hypoglycaemia, weight loss, reduced decline in eGFR, and increased reduction in albuminuria.

#### Contributors

KRT, MCL, and FTB contributed to the trial design. KRT, RSB, and BR were trial investigators and participated in data collection. FTB was responsible for medical oversight during the trial. FTB and AGZ were responsible for the statistical considerations in the analysis and trial design. All authors participated in critical review and interpretation of the data for the report. FTB and AGZ are the guarantors of this work and, as such, take responsibility for the integrity of the data and the accuracy of the data analysis.

#### Declaration of interests

KRT is a consultant for Eli Lilly and Company, Boehringer Ingelheim, Gilead Sciences, and AstraZeneca. BR is part of advisory boards for Boehringer Ingelheim and AstraZeneca, part of speakers' bureaux for Servier, Novartis, and Cipla, and was a clinical trial investigator for Litha. RSB is on advisory boards for Boehringer Ingelheim, Janssen, Novo Nordisk, and Sanofi, was part of speakers' bureaux for Eli Lilly and Company, Boehringer Ingelheim, Sanofi, Regeneron, AstraZeneca, and Amarin, and has received research support from Amgen, Novo Nordisk, Janssen, Amarin, AstraZeneca, Eisai, and Sanofi. MCL, DBW, and FTB are employees and shareholders of Eli Lilly and Company and have a patent pending for the use of dulaglutide for chronic kidney disease. AGZ was an employee and shareholder of Eli Lilly and Company at the time that this study was done and has a patent pending for the use of dulaglutide for chronic kidney disease.

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