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# Efficacy and hypoglycaemia outcomes with once-weekly insulin icodec versus once-daily basal insulin in individuals with type 2 diabetes by kidney function: A post hoc participant-level analysis of the ONWARDS 1–5 trials

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## Abstract

**Aim:** This post hoc analysis of ONWARDS 1–5 assessed the efficacy and hypoglycaemia outcomes with once-weekly insulin icodec (icodec) versus once-daily basal insulin comparators (degludec, glargine U100 or glargine U300) in insulin-naive (ONWARDS 1, 3 and 5) and insulin-experienced (ONWARDS 2 and 4) adults (aged ≥18 years) with type 2 diabetes (T2D) by kidney function subgroup.

**Materials and Methods:** Treatment outcomes were analysed by trial according to kidney function subgroup (estimated glomerular filtration rate [eGFR] ≥90; eGFR 60–<90; eGFR 30–<60; eGFR <30; all mL/min/1.73m$^2$). Severe kidney function impairment (eGFR <30) at screening was an exclusion criterion for ONWARDS 1–4, but not ONWARDS 5.

**Results:** ONWARDS 1–5 included 3765 participants; 3763 were included in this analysis. In ONWARDS 1, 3 and 5, there were no statistically significant treatment interactions by kidney function subgroup for change in glycated haemoglobin (HbA1c) from baseline to end of treatment (EOT); there were statistically significant subgroup interactions in ONWARDS 2 and 4 (both *p*-interaction <0.05). Change in body weight (baseline to EOT) across kidney function subgroups was comparable between treatment arms. Across trials, there was no consistent trend by kidney function subgroup for mean weekly insulin dose during the last 2 weeks of treatment or rates of combined clinically significant or severe hypoglycaemia. There were no

statistically significant treatment interactions by kidney function subgroup for the achievement of HbA1c <7% without clinically significant or severe hypoglycaemia; all *p*-interaction >0.05.

**Conclusions:** Efficacy and hypoglycaemia outcomes of icodec versus once-daily comparators were generally consistent among adults with T2D, regardless of kidney function.

**KEYWORDS**
basal insulin, glycaemic control, hypoglycaemia, insulin analogues, type 2 diabetes

## 1 | INTRODUCTION

In type 2 diabetes (T2D), impaired glucose homeostasis affects multiple major organs, including the kidneys.[1] This can lead to diminished kidney function, which is associated with reduced insulin clearance, prolonged insulin activity and reduced insulin requirements as estimated glomerular filtration rate (eGFR) declines.[2–4] Taken together, this results in a substantially increased risk of hypoglycaemia in people with impaired kidney function who are using insulin.[5,6] Therefore, assessment of the efficacy and safety of novel insulin products in people with T2D across a spectrum of kidney function levels is warranted.[7]

Insulin icodec (icodec) is a basal insulin analogue suitable for once-weekly administration.[8,9] Previously, the impact of kidney function impairment on the pharmacokinetic profile of icodec was investigated in 58 individuals without diabetes with varying levels of kidney function impairment (normal kidney function [eGFR ≥90 mL/min/1.73m$^2$]: $n = 12$; mild kidney function impairment [eGFR 60 to <90 mL/min/1.73m$^2$]: $n = 12$; moderate kidney function impairment [eGFR 30 to <60 mL/min/1.73m$^2$]: $n = 12$; severe kidney function impairment [eGFR <30 mL/min/1.73m$^2$]: $n = 12$; and end-stage kidney disease [individuals requiring haemodialysis treatment]: $n = 10$).[10] Similar to what has been observed for other basal insulins, icodec exposure (i.e., the serum concentration of icodec) trended numerically slightly higher in individuals with any level of kidney function impairment compared with those who had normal kidney function.[10–12] The study concluded that, because icodec is already dosed according to each individual's needs, no specific adjustment of icodec should be made in individuals with kidney function impairment.[10] However, clinical data on the efficacy and safety of icodec by kidney function impairment have not been published.

The ONWARDS phase 3a clinical trial programme included five trials (ONWARDS 1–5) which investigated the efficacy and safety of icodec against once-daily (OD) comparators in individuals across the spectrum of T2D, and in a variety of clinical scenarios (ClinicalTrials.gov: NCT04460885; NCT04770532; NCT04795531; NCT04880850; NCT04760626).[13–17] In these trials, icodec demonstrated non-inferior and/or superior reductions in glycated haemoglobin (HbA1c) versus OD comparators, with comparable rates of hypoglycaemia. This post hoc analysis of ONWARDS 1–5 assessed the efficacy and hypoglycaemia outcomes with once-weekly icodec versus OD basal comparators in insulin-naive and insulin-experienced adults with T2D according to kidney function subgroup.

## 2 | MATERIALS AND METHODS

### 2.1 | Trial design and participants

The ONWARDS 1–5 trial designs have been published; key points are summarized in this section.[8,13–17] ONWARDS 1–5 investigated the efficacy and safety of icodec in insulin-naive (ONWARDS 1, 3 and 5) or insulin-experienced (ONWARDS 2 and 4) adults (aged ≥18 years) with T2D. All five trials were randomized, multicentre, phase 3a trials with a treatment period of 26 weeks (ONWARDS 2–4) or 52 weeks (ONWARDS 1 and 5). ONWARDS 1 had a 26-week extension phase, data from which are included in this analysis. As such, the planned time to end of treatment (EOT) differed between trials (ONWARDS 1, week 78; ONWARDS 2–4, week 26; ONWARDS 5, week 52).

Key eligibility criteria for ONWARDS 1–5 included an HbA1c at screening between 7.0% (53 mmol/mol) and 10.0% (86 mmol/mol; ONWARDS 2 and 4), or 11.0% (97 mmol/mol; ONWARDS 1 and 3) or no upper limit (ONWARDS 5). Severe kidney function impairment (eGFR <30 mL/min/1.73m$^2$) at screening was an exclusion criterion in ONWARDS 1–4; ONWARDS 5 incorporated real-world elements to better reflect clinical practice, and had no inclusion or exclusion criteria for kidney function impairment.[17] Across the trials, treatment with background non-insulin glucose-lowering medication was permitted; however, the use of sulphonylureas and glinides was either discontinued at randomization (ONWARDS 1, 2 and 4) or the dose was reduced by 50% (ONWARDS 3 and 5).[8] For ONWARDS 4, eligible participants were already on a pretrial basal-bolus regimen.[8]

In ONWARDS 1–4, eligible participants were randomized (1:1) to icodec or an OD insulin comparator (degludec: ONWARDS 2 and 3; glargine U100: ONWARDS 1 and 4). In ONWARDS 4, participants in both arms also received 2–4 daily injections of insulin aspart.[8,16] Participants in ONWARDS 5 were randomized (1:1) to icodec with a dosing guide app or an OD comparator (degludec, glargine U100 or glargine U300 at the investigators' discretion).[8] In insulin-naive participants (ONWARDS 1, 3 and 5), the starting dose of icodec was 70 U/week. For those individuals switching to icodec in ONWARDS 2 and 4, the weekly icodec dose was calculated as the participant's pretrial

basal insulin dose multiplied by seven. A 50% one-time additional dose was administered with the first injection,[8] and the calculated once-weekly dose was administered from the second injection.

In ONWARDS 1–4, icodec and OD insulin comparator doses were titrated weekly based on pre-breakfast self-measured blood glucose values (target: 80–130 mg/dL [4.4–7.2 mmol/L]).[8] In ONWARDS 5, icodec titration was guided by the dosing guide app, while OD comparator doses were titrated at the investigators' discretion, as per standard clinical practice.[17]

During ONWARDS 1, 2 and 4, participants wore a continuous glucose monitoring (CGM) device (Dexcom G6) at prespecified 4-week intervals (weeks 0–4 [ONWARDS 1, 2 and 4], weeks 22–26 [ONWARDS 1, 2 and 4], weeks 48–52 [ONWARDS 1] and weeks 74–78 [ONWARDS 1]); CGM data were not collected in ONWARDS 3 and 5. CGM data were blinded to the participant and the investigator, and not used for the reporting of hypoglycaemic episodes or to aid insulin dose titration.[8]

## 2.2 | Outcomes

The following treatment outcomes were analysed by trial across kidney function subgroups: change in HbA1c from baseline to planned EOT; CGM metrics during the last 4 weeks of treatment (ONWARDS 1, 2 and 4), including the proportion of time in range (TIR; 70–180 mg/dL [3.9–10.0 mmol/L]), the proportion of time above range (TAR; >180 mg/dL [>10.0 mmol/L]) and the proportion of time below range (TBR; <70 mg/dL [<3.9 mmol/L] and <54 mg/dL [<3.0 mmol/L]); change in body weight from baseline to planned EOT; mean weekly insulin dose during the last 2 weeks of treatment; the number of episodes of clinically significant hypoglycaemia (level 2; blood glucose level: <54 mg/dL [<3.0 mmol/L], confirmed by blood glucose meter) or severe hypoglycaemia (level 3; hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery) from baseline to week 83 (ONWARDS 1), to week 31 (ONWARDS 2–4) or to week 57 (ONWARDS 5); and the achievement of HbA1c <7.0% at EOT without clinically significant or severe hypoglycaemia in the previous 12 weeks.

Kidney function subgroups were based on eGFR at screening: normal kidney function (eGFR ≥90 mL/min/1.73 $m^2$); mild kidney function impairment (eGFR 60–<90 mL/min/1.73 $m^2$); moderate kidney function impairment (eGFR 30–<60 mL/min/1.73 $m^2$); and severe kidney function impairment (eGFR <30 mL/min/1.73 $m^2$). eGFR was calculated based on a participant's creatinine value using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Baseline characteristics and rates of hypoglycaemia in participants who had hypoalbuminaemia (baseline serum albumin: <35 g/L) were summarized descriptively.

## 2.3 | Statistical analyses

The statistical methods used in ONWARDS 1–5 have been published previously.[8,13–17]

Across all statistical analyses, the following standard fixed factors were used: treatment, region, personal continuous glucose-monitoring device use (yes or no) (ONWARDS 2 and 4 only), use of sulfonylureas or glinides (yes or no) (ONWARDS 3 only), kidney function impairment subgroup and treatment by subgroup interaction. Changes in HbA1c and body weight from baseline to planned EOT were analysed using an analysis of covariance (ANCOVA) model, with standard fixed factors and the baseline response as a covariate. CGM end-points (TIR and TAR) were analysed using an analysis of variance (ANOVA) model with standard fixed factors. The composite assessment (achievement of HbA1c <7.0% without clinically significant or severe hypoglycaemia) was analysed using a logistic regression model with log-link function, standard fixed factors and the baseline HbA1c value as a covariate. Missing values were imputed using multiple imputation. Sensitivity analyses were not performed.

# 3 | RESULTS

## 3.1 | Trial participants

Of the 3765 participants in ONWARDS 1–5, 3763 had eGFR measurements at screening and were included in this analysis. Overall, 1875 participants (49.8%) had normal kidney function, 1450 (38.5%) had mild kidney function impairment, 429 (11.4%) had moderate kidney function impairment and eight (0.2%) had severe kidney function impairment (Table 1). At baseline, HbA1c values were broadly similar for each kidney function subgroup across trials. Generally, participants in the mild and moderate kidney function impairment subgroups had a numerically higher mean duration of T2D at baseline than those in the normal kidney function subgroup.

## 3.2 | Glycaemic outcomes

Estimated treatment differences (ETD) in change in HbA1c from baseline to EOT by kidney function subgroup are summarized in Figure 1. In ONWARDS 1, 3 and 5, there were no statistically significant treatment interactions by kidney function subgroup for change in HbA1c from baseline to planned EOT; however, in ONWARDS 2 and 4, there were statistically significant subgroup interactions ($p$-interaction <0.05 for both trials). In ONWARDS 2 and 4, participants with normal kidney function or with moderate kidney function impairment had either a numerically or statistically significantly larger reduction in HbA1c with icodec versus the OD comparator, whereas those with mild kidney function impairment had either a comparable or statistically significantly larger reduction in HbA1c with the OD comparator versus icodec. Hence, no clinically relevant pattern was observed.

In ONWARDS 1, 2 and 4, the observed proportions of TIR and TAR from week 74 to week 78 (ONWARDS 1) and from week 22 to week 26 (ONWARDS 2 and 4) showed no consistent trends by kidney function subgroup across trials (Supplementary Figure 1). There was no statistically significant treatment by subgroup interactions for proportion of TIR or TAR by kidney function subgroup ($p$-interaction >0.05 for all three trials) (Table 2).

**TABLE 1** Baseline characteristics for the ONWARDS 1–5 participants by kidney function.

| | ONWARDS 1 (insulin-naive) | | ONWARDS 3 (insulin-naive) | | ONWARDS 5 (insulin-naive) | | ONWARDS 2 (basal switch) | | ONWARDS 4 (basal-bolus) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Icodec ($n = 492$) | Glargine U100 ($n = 492$) | Icodec ($n = 293$) | Degludec ($n = 294$) | Icodec with app ($n = 542$) | OD insulin analogues[a] ($n = 542$) | Icodec ($n = 263$) | Degludec ($n = 263$) | Icodec + aspart ($n = 291$) | Glargine U100 + aspart ($n = 291$) |
| Normal kidney function (eGFR ≥ 90 mL/min/1.73m$^2$) | | | | | | | | | | |
| *n* | 224 | 222 | 173 | 185 | 311 | 307 | 94 | 109 | 123 | 127 |
| Sex, male, *n* (%) | 127 (56.7) | 104 (46.8) | 100 (57.8) | 112 (60.5) | 175 (56.3) | 164 (53.4) | 47 (50.0) | 53 (48.6) | 61 (49.6) | 60 (47.2) |
| Age, mean (SD), years | 54.9 (9.7) | 54.8 (9.8) | 53.1 (8.9) | 55.6 (9.2) | 54.8 (9.9) | 55.5 (9.3) | 57.4 (9.6) | 58.9 (7.7) | 54.6 (10.3) | 55.5 (9.3) |
| Body weight, mean (SD), kg | 86.1 (17.5) | 83.9 (16.9) | 82.0 (20.2) | 81.2 (18.3) | 93.2 (23.2) | 95.3 (23.2) | 88.0 (18.4) | 81.1 (16.2) | 87.1 (18.9) | 82.9 (18.0) |
| Duration of T2D, mean (SD), years | 10.3 (5.6) | 10.5 (5.5) | 9.8 (5.7) | 10.5 (5.7) | 10.5 (5.9) | 10.5 (6.6) | 15.0 (7.8) | 15.6 (7.2) | 14.0 (7.8) | 13.7 (6.1) |
| HbA1c, mean (SD), % | 8.67 (1.01) | 8.58 (1.02) | 8.61 (1.11) | 8.60 (0.99) | 9.14 (1.73) | 9.08 (1.63) | 8.33 (0.91) | 8.20 (0.77) | 8.47 (0.84) | 8.51 (0.97) |
| eGFR, mean (SD), mL/min/1.73m$^2$ | 101.6 (8.4) | 102.2 (9.2) | 104.1 (9.5) | 101.7 (8.5) | 102.8 (9.3) | 102.2 (9.2) | 99.8 (8.6) | 99.0 (6.6) | 101.6 (9.1) | 100.5 (8.6) |
| Mild kidney function impairment (eGFR 60–<90 mL/min/1.73m$^2$) | | | | | | | | | | |
| *n* | 223 | 213 | 97 | 88 | 174 | 171 | 135 | 108 | 121 | 120 |
| Sex, male, *n* (%) | 136 (61.0) | 128 (60.1) | 66 (68.0) | 56 (63.6) | 103 (59.2) | 106 (62.0) | 91 (67.4) | 59 (54.6) | 70 (57.9) | 66 (55.0) |
| Age, mean (SD), years | 61.8 (8.7) | 61.1 (8.5) | 64.1 (8.0) | 62.9 (8.8) | 63.9 (9.2) | 62.7 (8.7) | 63.6 (8.2) | 64.4 (8.4) | 62.9 (8.3) | 62.7 (8.9) |
| Body weight, mean (SD), kg | 83.7 (17.7) | 85.2 (18.4) | 89.6 (18.3) | 87.2 (17.4) | 92.6 (21.8) | 92.0 (18.7) | 80.8 (18.2) | 79.9 (16.1) | 82.5 (17.1) | 82.7 (17.3) |
| Duration of T2D, mean (SD), years | 12.3 (7.0) | 12.1 (7.7) | 12.5 (7.1) | 12.6 (7.1) | 13.6 (7.9) | 13.0 (7.2) | 16.8 (8.4) | 17.6 (8.3) | 20.2 (9.2) | 18.7 (8.4) |
| HbA1c, mean (SD), % | 8.37 (0.97) | 8.36 (0.99) | 8.48 (1.14) | 8.21 (0.99) | 8.70 (1.40) | 8.64 (1.28) | 8.10 (0.69) | 8.04 (0.82) | 8.19 (0.87) | 8.15 (0.78) |
| eGFR, mean (SD), mL/min/1.73m$^2$ | 77.7 (8.7) | 76.2 (8.4) | 78.3 (8.6) | 76.7 (8.3) | 75.6 (8.6) | 77.3 (8.7) | 76.3 (8.6) | 74.8 (8.9) | 74.1 (8.3) | 74.1 (8.9) |
| Moderate kidney function impairment (eGFR 30–<60 mL/min/1.73m$^2$)[b] | | | | | | | | | | |
| *n* | 45 | 57[b] | 23 | 21 | 52 | 61 | 34 | 46 | 47 | 44 |
| Sex, male, *n* (%) | 32 (71.1) | 31 (54.4) | 18 (78.3) | 16 (76.2) | 29 (55.8) | 41 (67.2) | 24 (70.6) | 28 (60.9) | 23 (48.9) | 24 (54.5) |
| Age, mean (SD), years | 66.2 (9.9) | 66.2 (7.8) | 66.1 (7.9) | 66.7 (6.9) | 67.7 (8.3) | 69.3 (7.7) | 71.2 (8.6) | 67.1 (6.7) | 64.7 (7.9) | 65.1 (9.2) |
| Body weight, mean (SD), kg | 87.9 (19.3) | 82.9 (17.4) | 96.4 (20.1) | 84.6 (18.8) | 96.5 (21.1) | 96.2 (19.5) | 83.6 (17.6) | 86.5 (20.7) | 89.0 (14.4) | 84.7 (15.1) |
| Duration of T2D, mean (SD), years | 15.2 (7.7) | 13.0 (7.1) | 15.7 (7.6) | 15.6 (9.1) | 14.2 (7.6) | 16.8 (10.7) | 19.7 (9.0) | 18.5 (8.3) | 22.7 (8.1) | 17.4 (7.5) |

**TABLE 1** (Continued)

| | ONWARDS 1 (insulin-naive) | | ONWARDS 3 (insulin-naive) | | ONWARDS 5 (insulin-naive) | | ONWARDS 2 (basal switch) | | ONWARDS 4 (basal-bolus) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Icodec ($n = 492$) | Glargine U100 (n = 492) | Icodec ($n = 293$) | Degludec ($n = 294$) | Icodec with app ($n = 542$) | OD insulin analogues[a] ($n = 542$) | Icodec ($n = 263$) | Degludec ($n = 263$) | Icodec + aspart ($n = 291$) | Glargine U100 + aspart ($n = 291$) |
| HbA1c, mean (SD), % | 8.34 (0.95) | 8.22 (1.07) | 8.42 (1.08) | 8.62 (1.16) | 8.83 (1.56) | 8.63 (1.22) | 7.98 (0.64) | 8.00 (0.67) | 8.06 (0.82) | 8.18 (0.88) |
| eGFR, mean (SD), mL/min/1.73m$^2$ | 50.2 (7.2) | 50.1 (7.6) | 48.0 (6.8) | 47.8 (7.3) | 48.1 (7.9) | 50.0 (7.2) | 47.9 (9.1) | 48.6 (7.7) | 50.6 (6.8) | 49.4 (7.8) |
| Severe kidney function impairment (eGFR < 30 mL/min/1.73m$^2$) | | | | | | | | | | |
| *n* | 0 | 0 | 0 | 0 | 5 | 3 | 0 | 0 | 0 | 0 |
| Sex, male, *n* (%) | - | - | - | - | 2 (40.0) | 2 (66.7) | - | - | - | - |
| Age, mean (SD), years | - | - | - | - | 71.8 (9.5) | 66.7 (9.5) | - | - | - | - |
| Body weight, mean (SD), kg | - | - | - | - | 84.7 (17.6) | 103.4 (28.5) | - | - | - | - |
| Duration of T2D, mean (SD), years | - | - | - | - | 11.7 (7.5) | 13.4 (5.1) | - | - | - | - |
| HbA1c, mean (SD), % | - | - | - | - | 7.98 (0.65) | 8.23 (0.15) | - | - | - | - |
| eGFR, mean (SD), mL/min/1.73m$^2$ | - | - | - | - | 24.4 (3.7) | 24.7 (6.7) | - | - | - | - |

*Note*: For two individuals, eGFR was not measured at screening. Individuals with severe kidney function impairment were excluded from ONWARDS 1–4 and only included in ONWARDS 5. Kidney function categories were based on eGFR, calculated using the CKD-EPI creatinine equation.[25]

Abbreviations: aspart, insulin aspart; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; degludec, insulin degludec; eGFR, estimated glomerular filtration rate; glargine U100, insulin glargine U100; HbA1c, glycated haemoglobin; icodec, insulin icodec; OD, once-daily; SD, standard deviation; T2D, type 2 diabetes.

[a]In ONWARDS 5, participants in the comparator arm received once-daily degludec, glargine U100 or glargine U300 at the investigators' discretion.

[b]For ONWARDS 1, this includes moderate kidney function impairment ($n = 56$) and severe kidney function impairment ($n = 1$). One participant with severe kidney function impairment was erroneously randomized to receive treatment and was included in the moderate kidney function impairment subgroup for the purpose of this analysis.

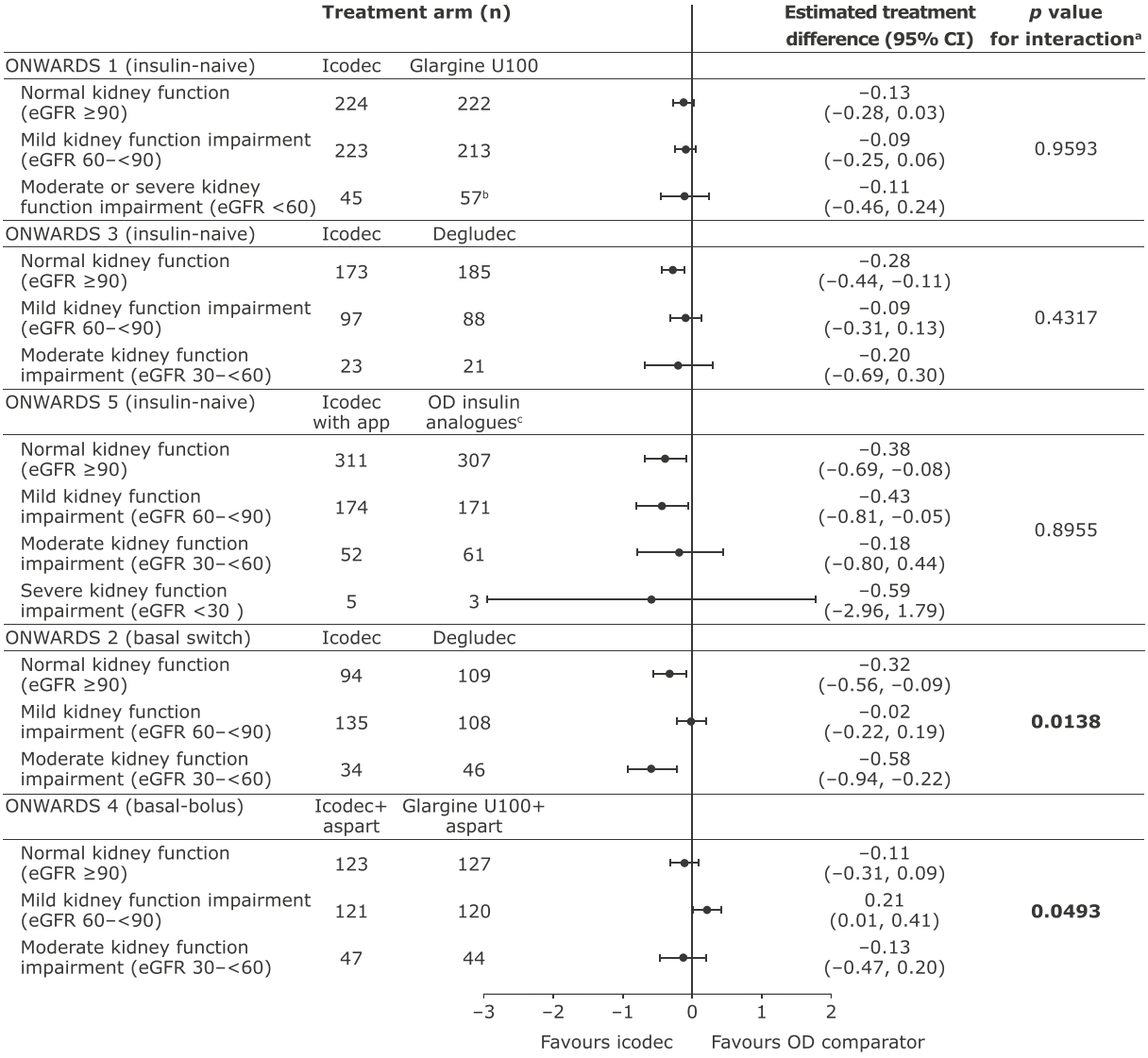


**FIGURE 1** Estimated treatment differences in change in HbA1c (%-points) from baseline to planned end of treatment by kidney function. Planned EOT: ONWARDS 1, week 78; ONWARDS 2–4, week 26; ONWARDS 5, week 52. For two individuals, eGFR was not measured at screening; all eGFR values are presented in mL/min/1.73m$^2$. Individuals with severe kidney function impairment were excluded from ONWARDS 1–4 and were only included in ONWARDS 5. Kidney function categories were based on eGFR, calculated using the CKD-EPI creatinine equation.[25] Change in HbA1c from baseline to planned EOT was analysed using an ANCOVA model, with treatment, region, kidney function impairment subgroup and treatment by subgroup interactions, and, if applicable, additional relevant factors as fixed factors, and the baseline response as a covariate. Bold values denote statistical significance at the $p < 0.05$ level. [a]Two-sided *p*-interaction value for the test of no treatment by kidney function subgroup interactions. [b]Includes moderate kidney function impairment ($n = 56$) and severe kidney function impairment ($n = 1$). In ONWARDS 1, one participant with severe kidney impairment was erroneously randomized to receive treatment and was included in the moderate kidney function impairment subgroup for the purpose of this analysis. [c]In ONWARDS 5, participants in the OD comparator arm received degludec, glargine U100 or glargine U300 at the investigators' discretion. ANCOVA, analysis of covariance; aspart, insulin aspart; CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; degludec, insulin degludec; eGFR, estimated glomerular filtration rate; EOT, end of treatment; glargine U100, insulin glargine U100; glargine U300, insulin glargine U300; HbA1c, glycated haemoglobin; icodec, insulin icodec; LCL, lower 95% confidence limit; OD, once-daily.

## 3.3 | Body weight and insulin dose

In all five trials, across normal, mild and moderate kidney function subgroups there was a small numerical difference in change in body weight from baseline to EOT that was comparable for icodec versus OD comparators (Supplementary Figure 2).

No consistent substantial differences were observed between kidney function subgroups in the mean weekly basal insulin doses for

**TABLE 2** Observed continuous glucose monitoring (CGM) values in participants from ONWARDS 1, 2 and 4 by kidney function.

| | ONWARDS 1 (insulin-naive) | | | | ONWARDS 2 (basal switch) | | | | ONWARDS 4 (basal-bolus) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Icodec | Glargine U100 | ETD (95% CI) | *p* value for interaction | Icodec | Degludec | ETD (95% CI) | *p* value for interaction | Icodec + aspart | Glargine U100 + aspart | ETD (95% CI) | *p* value for interaction |
| Time in range 70–180 mg/dL (3.9–10 mmol/L), % | | | | | | | | | | | | |
| Normal kidney function (eGFR ≥90) | 69.5 | 64.2 | 4.28 (0.59; 7.97) | 0.9174 | 65.3 | 59.6 | 4.07 (−1.21; 9.35) | 0.1079 | 66.4 | 64.2 | 1.71 (−2.60; 6.01) | 0.4962 |
| Mild kidney function impairment (eGFR 60–<90) | 70.1 | 65.5 | 4.22 (0.48; 7.96) | | 61.1 | 61.1 | −1.16 (−5.80; 3.48) | | 66.7 | 66.6 | 0.13 (−4.15; 4.41) | |
| Moderate kidney function impairment (eGFR 30–<60)[a] | 74.3 | 64.8 | 6.02 (−2.05; 14.10) | | 65.7 | 55.1 | 8.36 (−0.16; 16.89) | | 68.6 | 73.2 | −3.26 (−10.37; 3.84) | |
| Time above 180 mg/dL (>10.0 mmol/L), % | | | | | | | | | | | | |
| Normal kidney function (eGFR ≥90) | 29.3 | 34.9 | −4.63 (−8.41; −0.85) | 0.8885 | 32.9 | 39.4 | −4.73 (−10.14; 0.67) | 0.1080 | 30.9 | 33.4 | −1.90 (−6.31; 2.51) | 0.4932 |
| Mild kidney function impairment (eGFR 60–<90) | 28.9 | 33.7 | −4.30 (−8.13; −0.47) | | 37.8 | 38.3 | 0.70 (−4.05; 5.46) | | 30.7 | 31.4 | −0.67 (−5.06; 3.72) | |
| Moderate kidney function impairment (eGFR 30–<60)[a] | 24.3 | 34.5 | −6.52 (−14.79; 1.75) | | 33.0 | 44.3 | −8.98 (−17.71; −0.25) | | 28.7 | 24.3 | 3.23 (−4.05; 10.51) | |

*Note*: For two individuals, eGFR was not measured at screening; all eGFR values are presented in mL/min/1.73m$^2$. CGM values were assessed as observed means from week 74 to week 78 for ONWARDS 1, and week 22 to week 26 for ONWARDS 2 and 4; CGM data were not collected in ONWARDS 3 or 5. The percentage of time in the indicated glucose range is defined as 100 times the number of recorded measurements in each range, divided by the total number of recorded measurements. Kidney function subgroups were based on eGFR (mL/min/1.73m$^2$) at screening. CGM end-points were analysed using an ANOVA model with treatment, region, subgroup and treatment by subgroup interactions, and, if applicable, additional relevant factors as fixed factors.

Abbreviations: ANOVA, analysis of variance; aspart, insulin aspart; CGM, continuous glucose monitoring; CI, confidence interval; degludec, insulin degludec; eGFR, estimated glomerular filtration rate; ETD, estimated treatment difference; glargine U100, insulin glargine U100; icodec, insulin icodec.

[a]For ONWARDS 1, this includes moderate kidney function impairment ($n = 56$) and severe kidney function impairment ($n = 1$). One participant with severe kidney function impairment was erroneously randomized to receive treatment and was included in the moderate kidney function impairment subgroup for the purpose of this analysis.

**TABLE 3** Rates and incidence of hypoglycaemic events by kidney function.

| | ONWARDS 1 (insulin-naive) | | | | ONWARDS 3 (insulin-naive) | | | | ONWARDS 5 (insulin-naive) | | | | ONWARDS 2 (basal switch) | | | | ONWARDS 4 (basal-bolus) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Icodec | | Glargine U100 | | Icodec | | Degludec | | Icodec with app | | OD insulin analogues[a] | | Icodec | | Degludec + aspart | | Icodec | | Glargine U100 + aspart | |
| | N (%) | E (R) | N (%) | E (R) | N (%) | E (R) | N (%) | E (R) | N (%) | E (R) | N (%) | E (R) | N (%) | E (R) | N (%) | E (R) | N (%) | E (R) | N (%) | E (R) |
| Combined clinically significant or severe hypoglycaemia | | | | | | | | | | | | | | | | | | | | |
| Normal kidney function (eGFR ≥90) | 31 (13.8) | 58 (0.17) | 35 (15.8) | 67 (0.19) | 14 (8.1) | 35 (0.35) | 10 (5.4) | 16 (0.15) | 35 (11.3) | 47 (0.15) | 25 (8.2) | 39 (0.12) | 13 (13.8) | 42 (0.76) | 8 (7.3) | 18 (0.29) | 58 (47.2) | 414 (5.85) | 68 (53.5) | 370 (5.10) |
| Mild kidney function impairment (eGFR 60–<90) | 24 (10.8) | 155 (0.44) | 25 (11.7) | 43 (0.13) | 5 (5.2) | 10 (0.17) | 6 (6.8) | 7 (0.14) | 20 (11.5) | 45 (0.25) | 12 (7.1) | 32 (0.18) | 15 (11.2) | 53 (0.66) | 7 (6.5) | 12 (0.19) | 65 (53.7) | 381 (5.46) | 70 (58.3) | 384 (5.47) |
| Moderate kidney function impairment (eGFR 30–<60)[b] | 6 (13.3) | 14 (0.21) | 10 (17.5) | 11 (0.13) | 7 (30.4) | 8 (0.63) | 2 (9.5) | 2 (0.17) | 8 (15.4) | 11 (0.21) | 8 (13.1) | 10 (0.16) | 9 (26.5) | 18 (0.91) | 4 (8.7) | 12 (0.45) | 27 (57.4) | 149 (5.55) | 24 (54.5) | 184 (7.67) |
| Severe kidney function impairment (eGFR <30) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 1 (20.0) | 1 (0.20) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) |
| Severe hypoglycaemia | | | | | | | | | | | | | | | | | | | | |
| Normal kidney function (eGFR ≥90) | 1 (0.4) | 1 (0.003) | 2 (0.9) | 3 (0.009) | 0 (–) | 0 (–) | 1 (0.5) | 1 (0.009) | 0 (–) | 0 (–) | 3 (1.0) | 4 (0.01) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 2 (1.6) | 5 (0.07) | 1 (0.8) | 2 (0.03) |
| Mild kidney function impairment (eGFR 60–<90) | 0 (–) | 0 (–) | 2 (0.9) | 2 (0.006) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 2 (1.7) | 2 (0.03) | 0 (–) | 0 (–) |
| Moderate kidney function impairment (eGFR 30–<60) | 0 (–) | 0 (–) | 2 (3.5) | 2 (0.02) | 0 (–) | 0 (–) | 1 (4.8) | 1 (0.08) | 0 (–) | 0 (–) | 1 (1.6) | 1 (0.02) | 0 (–) | 0 (–) | 1 (2.2) | 1 (0.04) | 0 (–) | 0 (–) | 1 (2.3) | 1 (0.04) |
| Severe kidney function impairment (eGFR <30) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) | 0 (–) |

*Note*: For two individuals, eGFR was not measured at screening; all eGFR values are presented in mL/min/1.73m$^2$. Individuals with severe kidney function impairment were excluded from ONWARDS 1–4 and were only included in ONWARDS 5. Kidney function categories were based on eGFR, calculated using the CKD-EPI creatinine equation.[25] Clinically significant hypoglycaemia: blood glucose level of <54 mg/dL (<3.0 mmol/L), confirmed by blood glucose meter. Severe hypoglycaemia: hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery.

Abbreviations: aspart, insulin aspart; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; degludec, insulin degludec; E, number of hypoglycaemic events; eGFR, estimated glomerular filtration rate; glargine U100, insulin glargine U100; icodec, insulin icodec; OD, once-daily; PYE, patient-year of exposure (1 PYE = 365.25 days); R, rate of hypoglycaemia (number of events per PYE).

[a]In ONWARDS 5, participants in the OD comparator arm received degludec, glargine U100 or glargine U300 at the investigators' discretion.

[b]For ONWARDS 1, this includes moderate kidney function impairment ($n = 56$) and severe kidney function impairment ($n = 1$). One participant with severe kidney function impairment was erroneously randomized to receive treatment and was included in the moderate kidney function impairment subgroup for the purpose of this analysis.

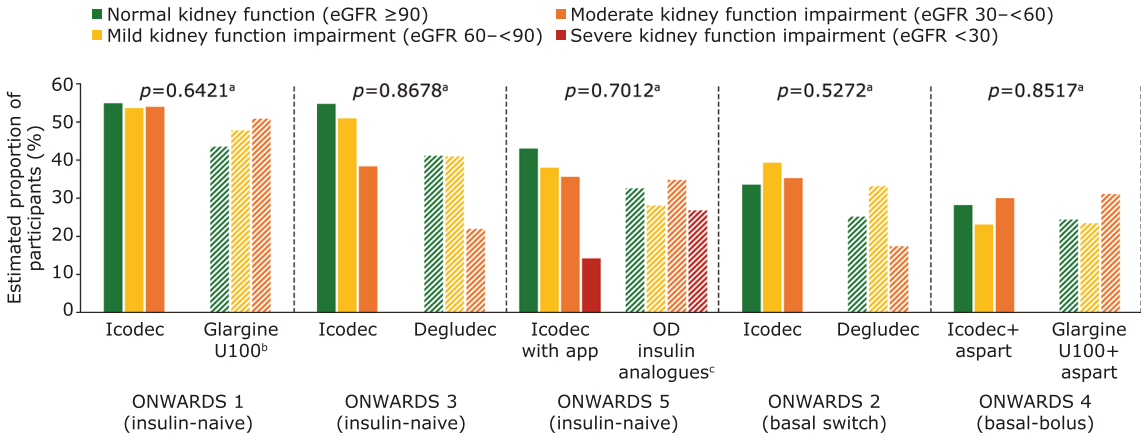


**FIGURE 2** Estimated proportion of participants who achieved HbA1c <7.0% at end of treatment (EOT) without clinically significant or severe hypoglycaemia in the previous 12 weeks by kidney function. Planned EOT: ONWARDS 1, week 78; ONWARDS 2–4, week 26; ONWARDS 5, week 52. For two individuals, eGFR was not measured at screening; all eGFR values are presented in mL/min/1.73m$^2$. In the severe kidney function impairment subgroup of ONWARDS 5, one of five participants receiving icodec with app and one of three participants receiving an OD comparator achieved HbA1c <7.0% at EOT without clinically significant or severe hypoglycaemia in the prior 12 weeks. Individuals with severe kidney function impairment were excluded from ONWARDS 1–4 and only included in ONWARDS 5. Kidney function categories were based on eGFR, calculated using the CKD-EPI creatinine equation.[25] Clinically significant hypoglycaemia: blood glucose level of <54 mg/dL (<3.0 mmol/L), confirmed by blood glucose meter. Severe hypoglycaemia: hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery. The achievement of HbA1c <7.0% without clinically significant or severe hypoglycaemia was analysed using a logistic regression model with log-link function with treatment, region, subgroup and treatment by subgroup interaction as fixed factors, and the baseline HbA1c value used as a covariate. [a]*p*-interaction value for treatment by subgroup interaction. [b]In ONWARDS 1, a single participant with severe kidney function impairment was erroneously randomized to receive treatment and was included in the moderate kidney function impairment subgroup for the purpose of this analysis. [c]In ONWARDS 5, participants in the OD comparator arm received degludec, glargine U100 or glargine U300 at the investigators' discretion. Aspart, insulin aspart; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; degludec, insulin degludec; eGFR, estimated glomerular filtration rate; EOT, end of treatment; glargine U100, insulin glargine U100; glargine U300, insulin glargine U300; HbA1c, glycated haemoglobin; icodec, insulin icodec; OD, once-daily.

icodec versus OD comparators during the last 2 weeks of treatment in ONWARDS 1, 2 and 3 (Supplementary Table S1).

## 3.4 | Hypoglycaemia outcomes

Across trials, there was no consistent trend by kidney function subgroup for overall rates of combined clinically significant or severe hypoglycaemia (Table 3). In ONWARDS 1, 2, 3 and 5, rates of combined clinically significant or severe hypoglycaemia were low (<1 episode per patient-year of exposure [PYE]) across kidney function subgroups with icodec and OD comparators. Furthermore, in ONWARDS 4 (basal-bolus trial), rates of combined clinically significant or severe hypoglycaemia were comparable across kidney function subgroups, and between treatment arms (icodec: 5.46–5.85 episodes per PYE; glargine U100: 5.10–7.67 episodes per PYE). In the ONWARDS 5 severe kidney function impairment subgroup, one of the five participants receiving icodec with app reported a clinically significant hypoglycaemic episode (no severe hypoglycaemic episodes were reported in any of the five participants); none of the three participants in the OD comparator arm reported a clinically significant or severe hypoglycaemic episode.

Across all kidney function subgroups and in both treatment arms in ONWARDS 1–5, the number of severe hypoglycaemic episodes reported was low (Table 3); eight severe hypoglycaemic episodes were observed with icodec and 18 were observed with OD comparators. No consistent trend was observed across kidney function subgroups in ONWARDS 1–5.

## 3.5 | Composite assessment

In general, across all trials and kidney function subgroups, there was a pattern towards a higher estimated proportion of participants achieving HbA1c <7% at EOT without clinically significant or severe hypoglycaemic episodes in the prior 12 weeks with icodec versus OD comparators (Figure 2). There were no statistically significant treatment interactions by kidney function subgroup for the composite assessment (all *p*-interactions >0.05).

## 3.6 | Hypoalbuminaemia

Of the 1881 participants across ONWARDS 1–5 who received icodec, three (0.2%) reported hypoalbuminaemia (serum albumin: <35 g/L): one participant from ONWARDS 1 (insulin-naive; aged 58 years; baseline HbA1c: 9.6%; baseline eGFR: 116 mL/min/1.73 m$^2$), one participant from ONWARDS 4 (basal-bolus regimen; aged 67 years;

baseline HbA1c: 8.8%; baseline eGFR: 80 mL/min/1.73 $m^2$) and one participant from ONWARDS 5 (insulin-naive; aged 62 years; baseline HbA1c: 8.1%; baseline eGFR: 80 mL/min/1.73 $m^2$). The participant from ONWARDS 1 withdrew consent after 16 weeks of treatment, with a change in HbA1c of −1.1%-points from baseline and no reported episodes of hypoglycaemia; at week 16, their weekly icodec dose was 3.5 U/kg (approximately 0.5 U/kg/day). The participant from ONWARDS 4 had a change in HbA1c of −1.2%-points from baseline to planned EOT and reported two episodes of clinically significant hypoglycaemia from baseline to week 31. During the last 2 weeks of treatment, the mean weekly icodec dose for this participant was 5.3 U/kg (approximately 0.8 U/kg/day). The participant from ONWARDS 5 had a change in HbA1c of −2.1%-points from baseline to planned EOT with no reported episodes of hypoglycaemia; their mean weekly icodec dose during the last 2 weeks of treatment was 1.2 U/kg (approximately 0.2 U/kg/day).

Of the 1882 participants across ONWARDS 1–5 who received OD comparators, four (0.2%) reported hypoalbuminaemia: one participant from ONWARDS 1 (insulin-naive; aged 56 years; baseline HbA1c: 8.7%; baseline eGFR: 102 mL/min/1.73 $m^2$) and three participants from ONWARDS 5 (all insulin-naive; aged 50, 52 and 56 years with baseline HbA1c levels of 10.2%, 9.2% and 10.6%, and baseline eGFR values of 90 mL/min/1.73 $m^2$, 98 mL/min/1.73 $m^2$ and 32 mL/min/1.73 $m^2$, respectively). The participant from ONWARDS 1 had a change in HbA1c of −2.8%-points from baseline, with no reported episodes of hypoglycaemia, and their mean weekly glargine U100 dose during the last 2 weeks of treatment was 4.2 U/kg (approximately 0.6 U/kg/day). Of the three participants from ONWARDS 5, the first had a change in HbA1c of −3.7%-points from baseline to planned EOT and reported one episode of clinically significant hypoglycaemia; during the last 2 weeks of treatment, their mean weekly insulin dose was 4.9 U/kg (approximately 0.7 U/kg/day). The second participant discontinued the trial and was lost to follow-up before receiving their first dose of treatment. The third participant withdrew from the trial after 26 weeks of treatment with a change in HbA1c of −1.7%-points and no reported episodes of hypoglycaemia; during the last 2 weeks of treatment, their mean weekly insulin dose was 1.1 U/kg (approximately 0.2 U/kg/day).

No participant with hypoalbuminaemia who was randomized to either treatment arm had severe hypoglycaemia.

## 4 | DISCUSSION

This post hoc analysis of data from the ONWARDS 1–5 trials demonstrated that the efficacy and hypoglycaemia outcomes of icodec versus OD insulin comparators were broadly consistent among insulin-naive and insulin-experienced adults with T2D who had a kidney function level ranging from normal function to severe impairment. However, very few participants with severe kidney function impairment were included. Notably, impaired kidney function did not impact the efficacy of icodec in terms of improvement in HbA1c in ONWARDS 1, 3 and 5 (insulin-naive population). Similar findings have been reported for other basal insulin analogues, including degludec, glargine U100 and glargine U300, which have also been found to be effective in reducing HbA1c across a variety of kidney function levels.[12,18,19] Here, a statistically significant treatment by subgroup interaction was found in ONWARDS 2 and 4 (insulin-experienced participants) for change in HbA1c from baseline. Whilst participants with mild kidney function impairment had either a comparable (ONWARDS 2) or lower (ONWARDS 4) reduction in HbA1c with icodec versus the OD comparator, findings in the normal kidney function and moderate kidney function impairment subgroups were in line with those from the respective global trials,[14,16] indicating no clear pattern between ETD in change in HbA1c and worsening kidney function in any of the trials. Additionally, in the present analysis, the proportion of participants achieving HbA1c <7.0% at EOT without clinically significant or severe hypoglycaemia in the icodec arm was higher than, or similar to, the OD comparator arm in ONWARDS 2 and 4, respectively, across all kidney function subgroups. Achievement of glycaemic control without increased risk of clinically significant or severe hypoglycaemia, as seen across the ONWARDS trials, including ONWARDS 2 and 4, is inherently beneficial for individuals with T2D receiving icodec, as it could potentially enhance treatment adherence. Previously, an analysis of patient-reported outcomes from ONWARDS 2 and 5 demonstrated improved treatment satisfaction and a strong preference for once-weekly versus once-daily basal insulin treatment, mainly owing to less frequent injections and ease of use, which could enhance treatment compliance and lead to improved glycaemic control.[20] Across trials, no consistent trend by kidney function subgroup for overall rates of combined clinically significant or severe hypoglycaemia was observed in the present analysis.

Rates of combined clinically significant or severe hypoglycaemia were low (<1 event per PYE) and broadly similar across normal, mild and moderate kidney function impairment subgroups in both icodec and OD comparator arms of the ONWARDS 1–3 and 5 trials in which participants received a basal-only insulin regimen. These results suggest that icodec can be used with no increased risk of clinically significant or severe hypoglycaemic episodes across individuals with normal, mild and moderate kidney function.

Across the ONWARDS 1, 2 and 4 trials, the observed TIR for icodec was generally similar to or higher than that of OD comparators, while the observed TAR for icodec was similar to or lower than that of OD comparators. This pattern was generally consistent across all kidney function impairment subgroups, suggesting that kidney function impairment did not impact CGM parameters in participants receiving icodec versus OD comparators. Furthermore, in the icodec arm of ONWARDS 1, mean TIR was greater than the internationally recommended target of 70%,[21] regardless of mild or moderate kidney function impairment.

Findings from previous studies of OD basal insulins suggest that lower insulin doses are required in individuals with more advanced kidney function impairment owing to reduced insulin clearance.[12,18] In the primary ONWARDS 1–5 trials, no consistent substantial differences were observed in the mean weekly dose of icodec versus OD comparators.[13–17] In the present analysis, no consistent substantial

differences were observed in the mean weekly dose of icodec compared with OD comparators across kidney function subgroups in ONWARDS 1, 2 and 3. This finding suggests that no specific dose adjustments are required for the administration of icodec in individuals with T2D who have kidney function impairment. Although, across ONWARDS 1–5 and in both treatment arms, there was a general trend towards lower mean weekly basal insulin doses with a lower eGFR. However, the ONWARDS 1–5 trials were optimized for between-arm rather than between-subgroup comparisons, and participants were not stratified by baseline eGFR upon randomization; therefore, between-subgroup differences and other confounding factors could impact comparisons made between subgroups within treatment arms, and the results should be considered in this context. It should be noted that for all insulin products, including icodec, dosing should be titrated to suit the needs of each individual.[22]

Although conclusions cannot be drawn based on the minimal data available from only three participants with hypoalbuminaemia who were randomized to icodec in ONWARDS 1–5, the hypoglycaemia data from these participants appear to be reassuring. Mechanistically, hypoalbuminaemia is unlikely to affect the hypoglycaemia profile of icodec. At steady state in individuals with a normal serum albumin level (35 to 50 g/L),[23] the maximum serum concentration of icodec is substantially lower than that of albumin; the ratio of albumin to icodec is approximately 2000:1, and so icodec molecules occupy less than 0.05% of all albumin molecules available in the serum.[9] Moreover, each albumin molecule has at least four high-affinity binding sites.[9] Therefore, an excess of binding sites exists in the circulating albumin pool even at relatively higher concentrations of icodec, and displacement of icodec from albumin due to reduced levels of albumin (e.g., from hypoalbuminaemia or albuminuria) will likely be minimal, with no clinically relevant effect on icodec activity.[9] However, further investigations in a larger population of individuals with this condition would be beneficial.

This analysis has several strengths, particularly the use of a dataset based on a large number of participants ($n = 3765$) from five different, randomized, multicentre, multinational trial populations covering the spectrum of T2D, including both insulin-naive and insulin-experienced individuals treated with basal-only or basal-bolus regimens. Therefore, the results are likely applicable to a range of populations with T2D. However, it should be noted that there are inherent limitations to this post hoc analysis which may limit the strength of any causal inferences made, namely that these assessments were not prespecified, and participants were not stratified by kidney function impairment subgroup at randomization. Indeed, most participants in ONWARDS 1–5 had normal kidney function (49.8%), and less than 1% of participants in ONWARDS 5 had severe kidney function impairment (severe kidney function impairment was an exclusion criterion for ONWARDS 1–4, as is common for phase 3 trials[24]). Therefore, the generalizability of the findings for individuals with T2D and severe kidney function impairment is limited. Validation of the present findings in further prospective studies could be beneficial. Furthermore, as the proportion of participants in each kidney function impairment subgroup varied between trials, the impact of differences in population, trial design and duration between ONWARDS 1–5 would likely be exaggerated in a meta-analysis, limiting its reliability and reducing the possibility of scientifically valid data interpretation. Thus, meta-analysis of the data by kidney function impairment subgroup was not performed. Similarly, supportive statistical analyses for hypoglycaemia outcomes could not be performed owing to the small number of hypoglycaemic episodes in each kidney function impairment subgroup. Longer follow-up studies could provide additional insights into the prolonged use of icodec in individuals with reduced kidney function.

In conclusion, the efficacy and hypoglycaemia outcomes with once-weekly icodec versus OD comparators were generally consistent among insulin-naive and insulin-experienced adults with T2D, regardless of kidney function. These findings suggest that no adjustments to the initiation dose or titration of icodec would be necessary based on kidney function.

## AUTHOR CONTRIBUTIONS

A combination of academic authors and authors who are employees of Novo Nordisk (the trial sponsor) participated in developing the trial concepts and design, and in collecting the data. All authors had full access to the data, participated in the critical review and drafting of the manuscript and were responsible for the decision to submit for publication.

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## CONFLICT OF INTEREST STATEMENT

Peter Rossing reports grants from AstraZeneca, Bayer and Novo Nordisk and has participated in advisory boards (all fees paid to institution) for AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Gilead Sciences, Lexicon Pharmaceuticals, Novo Nordisk and Sanofi. Malik Benamar and Christian Laugesen are employees of Novo Nordisk A/S. Alice Y.Y. Cheng has received consulting fees and honoraria for advisory board participation and speaking from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, GSK, HLS Therapeutics, Insulet, Janssen, Medtronic, Novo Nordisk, Pfizer, Sanofi and Takeda. Bharath Kumar is an employee of Novo Nordisk India Private Limited. Harpreet S. Bajaj reports trial fees paid to his institution by Novo Nordisk during ONWARDS 3 and ONWARDS 5; he also reports trial fees paid to his institution by Amgen, AstraZeneca, Boehringer Ingelheim, Ceapro, Eli Lilly and Company, Gilead Sciences, Ionis Pharmaceuticals, Janssen Pharmaceuticals, Kowa Pharmaceuticals Co. Ltd., Madrigal Pharmaceuticals, Merck, Novartis, Novo Nordisk, Pfizer, Sanofi and Tricida, outside of the submitted work.

## PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16231.

## DATA AVAILABILITY STATEMENT

Individual participant data will be shared in datasets in a de-identified/anonymized format. Shared data will include datasets from

clinical research sponsored by Novo Nordisk that was completed after 2001 for product indications approved in both the EU and the USA. The study protocol and the redacted clinical study report will be made available according to Novo Nordisk data-sharing commitments. These data will be available permanently after research completion and approval of product and product use in both the EU and the United States (no end date). Data will be shared with bona fide researchers who submit a research proposal requesting access to data for use as approved by the Independent Review Board according to its charter (see www.novonordisk-trials.com). These data can be accessed via an access request proposal form; the access criteria can be found at www.novonordisk-trials.com. The data will be made available on a specialized SAS data platform.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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