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Efficacy and hypoglycaemia outcomes with once-weekly insulin icodec versus once-daily basal insulin in type 2 diabetes according to baseline glucagon-like peptide-1 receptor agonist and sodium-glucose co-transporter-2 inhibitor use: A post hoc analysis of ONWARDS 1–5

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Abstract

Aims: To assess the treatment effects of once-weekly insulin icodec (icodec) versus once-daily basal insulin comparators in individuals with type 2 diabetes (T2D) according to baseline glucagon-like peptide-1 receptor agonist (GLP-1RA) and sodium-glucose co-transporter-2 inhibitor (SGLT2i) use.

Materials and Methods: This post hoc analysis of the randomized ONWARDS 1–5 trials of individuals with T2D assessed treatment outcomes by trial according to baseline GLP-1RA and/or SGLT2i use.

Results: At screening, 21.3% (801/3765) and 36.9% (1388/3765) of participants in ONWARDS 1–5 were treated with a GLP-1RA or an SGLT2i, respectively. Baseline characteristics were broadly similar across treatment arms irrespective of GLP-1RA/SGLT2i use; GLP-1RA users had numerically higher body mass indices than non-users. Across trials, there were no statistically significant treatment interactions by GLP-1RA or SGLT2i subgroups with respect to: change in glycated haemoglobin (HbA1c) and body weight from baseline to end of treatment (except for body weight change by SGLT2i use in ONWARDS 5); weekly basal insulin dose during the last 2 weeks of treatment (except SGLT2i use in ONWARDS 5); and achievement of HbA1c less than 7% without clinically significant or severe hypoglycaemia. Irrespective of GLP-1RA/SGLT2i use, the rates of clinically significant or severe hypoglycaemia were less than one episode per patient-year of exposure across all trials except ONWARDS 4 (basal-bolus trial).

Conclusions: The efficacy and hypoglycaemia profile of icodec versus once-daily comparators was generally consistent across ONWARDS trials irrespective of background GLP-1RA and/or SGLT2i use.

KEYWORDS
basal insulin, GLP-1 receptor agonist, glycaemic control, hypoglycaemia, SGLT2 inhibitor, type 2 diabetes

1 | INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose co-transporter-2 inhibitors (SGLT2is) are common therapies for individuals with type 2 diabetes (T2D).[1,2] The American Diabetes Association (ADA) and European Association for the Study of Diabetes recommend the use of GLP-1RAs and SGLT2is as first-line therapies for T2D after lifestyle changes to reduce blood glucose levels and improve cardiovascular and renal outcomes in individuals with T2D and established or high risk of atherosclerotic cardiovascular disease, heart failure and/or chronic kidney disease.[1,3,4]

Once-weekly insulin icodec (icodec) is a basal insulin analogue that may improve treatment adherence for individuals with T2D by reducing the number of yearly basal insulin injections from at least 365 to 52.[5] The efficacy and safety of icodec have been investigated in the ONWARDS phase 3a clinical development programme.[6] In the randomized ONWARDS 1–5 trials (NCT04460885, NCT04770532, NCT04795531, NCT04880850 and NCT04760626), the favourable efficacy and safety profile of once-weekly icodec, or icodec with a dosing guide app (ONWARDS 5), was demonstrated versus once-daily basal insulin comparators in insulin-naive or insulin-experienced participants with T2D in different clinical scenarios.[7–11] In all five trials, the background use of GLP-1RAs and/or SGLT2is was recommended to be continued throughout the trial, per protocol.[6–11] Recognizing individual characteristics that may influence the treatment response to icodec, such as concomitant use with GLP-1RAs or SGLT2is, is essential to optimize care for individuals with T2D.

Combination therapy of basal insulin with GLP-1RAs and/or SGLT2is is a well-established treatment approach to meet glycaemic targets in individuals with T2D as their disease progresses.[12] Although GLP-1RAs and SGLT2is are not associated with an increased risk of hypoglycaemia, it is important to consider the potential impact of these agents on glycaemic control, weight gain and insulin-induced hypoglycaemia when prescribed concomitantly with basal insulin.[1,12]

The aim of this post hoc analysis of ONWARDS 1–5 was to assess the treatment effects of once-weekly icodec versus once-daily basal insulin comparators according to baseline GLP-1RA and/or SGLT2i use in insulin-naive and insulin-experienced participants with T2D.

2 | MATERIALS AND METHODS

2.1 | Trial design and participants

The design of the ONWARDS 1–5 trials has been described previously.[6–11] In brief, ONWARDS 1–5 were randomized, multinational, multicentre trials that included insulin-naive (ONWARDS 1, 3 and 5) and insulin-experienced (ONWARDS 2 and 4) adults (aged ≥18 years) with T2D (Table S1). Participants were randomized (1:1) to once-weekly icodec (700 U/mL) or a once-daily basal insulin comparator (insulin glargine U100 [glargine U100; ONWARDS 1 and 4], insulin degludec [degludec; ONWARDS 2 and 3] or one of glargine U100, insulin glargine U300 or degludec [ONWARDS 5]). In ONWARDS 4 (basal-bolus insulin trial), participants in both treatment arms also received 2–4 daily bolus insulin aspart injections. The trial length varied between ONWARDS trials; the end of treatment (EOT) visit occurred at week 26 for ONWARDS 2–4, week 52 in ONWARDS 5 and week 78 in ONWARDS 1 (52-week main phase plus 26-week extension phase).

In ONWARDS 1–4, basal insulin dose titration occurred weekly based on pre-breakfast self-measured blood glucose values (target blood glucose range: 80–130 mg/dL [4.4–7.2 mmol/L]). In ONWARDS 5, icodec dose titration was aided by a dosing app, and comparator dose titration was at the investigator's discretion, according to clinical practice. In all five trials, pre-trial GLP-1RA and/or SGLT2i use was permitted if participants had received a stable dose for at least 90 days prior to the day of screening, and the dose was maintained during the trial period unless adjusted for safety reasons. Participants were not stratified by baseline GLP-1RA or SGLT2i use upon randomization.

The ONWARDS 1–5 trials were approved by independent ethics committees or institutional review boards and conducted in accordance with the principles of the Declaration of Helsinki[13] and the Good Clinical Practice guidelines of the International Council for Harmonisation. All participants provided informed consent before trial entry.

2.2 | Post hoc analysis

The following ONWARDS 1–5 treatment outcomes were assessed by trial according to GLP-1RA and/or SGLT2i use or non-use at baseline: change in glycated haemoglobin (HbA1c) from baseline to planned EOT; change in body weight from baseline to EOT; mean weekly basal insulin dose during the last 2 weeks of treatment; the number of episodes of clinically significant hypoglycaemia (blood glucose value of <54 mg/dL [3.0 mmol/L] confirmed by blood glucose meter) or severe hypoglycaemia (hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery); and the achievement of HbA1c under 7% (53 mmol/mol) at EOT without clinically significant or severe hypoglycaemic episodes in the previous 12 weeks (composite assessment).

2.3 | Statistical analyses

The statistical methods used in ONWARDS 1–5 have been published previously.[6–11] Efficacy endpoints were analysed using the full analysis set (FAS; all randomly assigned participants) and hypoglycaemic outcomes were summarised using the safety analysis set (SAS; all participants who received at least one treatment dose).

Across all statistical analyses, the following standard fixed factors were used: treatment, region, subgroup, treatment by subgroup interactions; additional relevant factors were used as fixed factors if applicable. Change in HbA1c and body weight from baseline to EOT were

analysed using an analysis of covariance (ANCOVA) of the FAS, with standard fixed factors and the baseline response as a covariate. An additional analysis of body weight at EOT relative to baseline was completed using an ANCOVA of the FAS based on log-transformed values with standard fixed factors and log-transformed baseline response as a covariate. The mean weekly basal insulin dose during the last 2 weeks of treatment was analysed using an ANCOVA of the FAS based on log-transformed values with standard fixed factors and log-transformed baseline response as a covariate (ONWARDS 2 and 4). Missing data in the aforementioned analyses were imputed using multiple imputation.

The number of clinically significant or severe hypoglycaemic episodes per patient-year of exposure (PYE) in the SAS were reported descriptively. The achievement of HbA1c under 7% (53 mmol/mol) without clinically significant or severe hypoglycaemic episodes in the FAS was analysed using a logistic regression model (logit link), with treatment, region, subgroup and treatment by subgroup interactions and, if applicable, additional relevant factors as fixed factors and the baseline HbA1c value as a covariate. Missing HbA1c measurements were imputed using the same method as specified for the primary analysis.

3 | RESULTS

3.1 | Participant disposition

At screening, of the 3765 participants in ONWARDS 1–5, 801 (21.3%) were treated with GLP-1RAs (icodec: 400/1882; comparators: 401/1883), and 1388 (36.9%) with SGLT2is (icodec: 711/1882; comparators: 677/1883). Among GLP-1RA and SGLT2i users, 385 (10.2% of total population) were treated with both a GLP-1RA and an SGLT2i (icodec: 194/1882; comparators: 191/1883).

Baseline characteristics of participants by trial and by concomitant therapies at baseline are presented in Table S2. Across treatment arms, baseline HbA1c values were generally similar or numerically lower in GLP-1RA or SGLT2i users versus non-users at baseline. Across all trials, participants who were treated with GLP-1RAs at baseline generally had a numerically greater mean body mass index (BMI) and a longer diabetes duration than participants who were not treated with GLP-1RAs. Participant BMI and diabetes duration at baseline were broadly similar for SGLT2i users and non-users between treatment arms across all trials. Among participants who were treated with both a GLP-1RA and an SGLT2i at baseline, HbA1c at baseline was broadly similar between the once-weekly icodec and once-daily comparator arms across trials (Table S3). The number of participants who discontinued GLP-1RA and/or SGLT2i use after screening was low across treatment arms and trials (Table S4).

3.2 | Change in HbA1c

The estimated treatment difference in HbA1c from baseline to EOT by baseline GLP-1RA and SGLT2i use is presented in Figure 1. Across all five trials, participants receiving icodec versus comparators had larger or similar reductions in mean HbA1c from baseline to EOT irrespective of GLP-1RA use; there was no statistically significant treatment by GLP-1RA subgroup interaction in HbA1c changes ($p > 0.05$ across trials). Participants in the icodec arm also had larger or similar reductions in mean HbA1c from baseline to EOT compared with the comparator arm irrespective of SGLT2i use, and there was no statistically significant treatment by SGLT2i subgroup interaction in HbA1c changes ($p > 0.05$ across trials).

A similar trend in mean HbA1c reduction from baseline to EOT for icodec versus comparators was observed in participants who were treated with both GLP-1RAs and SGLT2is at baseline (Table S5).

3.3 | Body weight and insulin dose

With the exception of ONWARDS 4, there were numerically greater changes in body weight from baseline to EOT in the icodec arm than in the comparator arm across trials, irrespective of GLP-1RA use (Figure 2A). However, there was no statistically significant treatment by GLP-1RA subgroup interaction for change in body weight from baseline to EOT in any trial ($p > 0.05$ across trials). Overall, in the additional analysis of body weight at EOT relative to baseline, the treatment ratio between icodec and comparators was similar between GLP-1RA use subgroups across all trials (GLP-1RA users vs. non-users: ONWARDS 1: 1.01 vs. 1.01; ONWARDS 2: 1.02 vs. 1.02; ONWARDS 3: 1.02 vs. 1.00; ONWARDS 4: 1.00 vs. 1.01; ONWARDS 5: 1.02 vs. 1.01).

Generally, the mean weekly basal insulin dose during the last 2 weeks of treatment was numerically higher in the icodec arm than in the comparator arm, regardless of GLP-1RA use (Table 1 and Table S6). There was no statistically significant treatment by GLP-1RA subgroup interaction for mean weekly basal insulin dose during the last 2 weeks of treatment in any trial ($p > 0.05$ across trials).

As in the GLP-1RA analysis, there were generally numerically greater changes in mean body weight from baseline to EOT in the icodec arm than in the comparator arm across trials, irrespective of SGLT2i use (except for non-users in ONWARDS 5 because there were numerically greater changes in body weight in the comparator arm than the icodec arm) (Figure 2B). There was no statistically significant treatment by SGLT2i subgroup interaction for change in mean body weight from baseline to EOT in any trial except for ONWARDS 5 ($p = 0.006$).

Generally, the mean weekly basal insulin dose during the last 2 weeks of treatment was similar or numerically higher in the icodec arm than in the comparator arm across baseline SGLT2i subgroups and treatment arms (Table 1 and Table S6). There was no statistically significant treatment by SGLT2i subgroup interaction for the mean weekly basal insulin dose during the last 2 weeks of treatment in any trial except for ONWARDS 5 ($p = 0.03$), in which there was a higher mean insulin dose in the icodec arm versus the comparator arm in users compared with non-users.

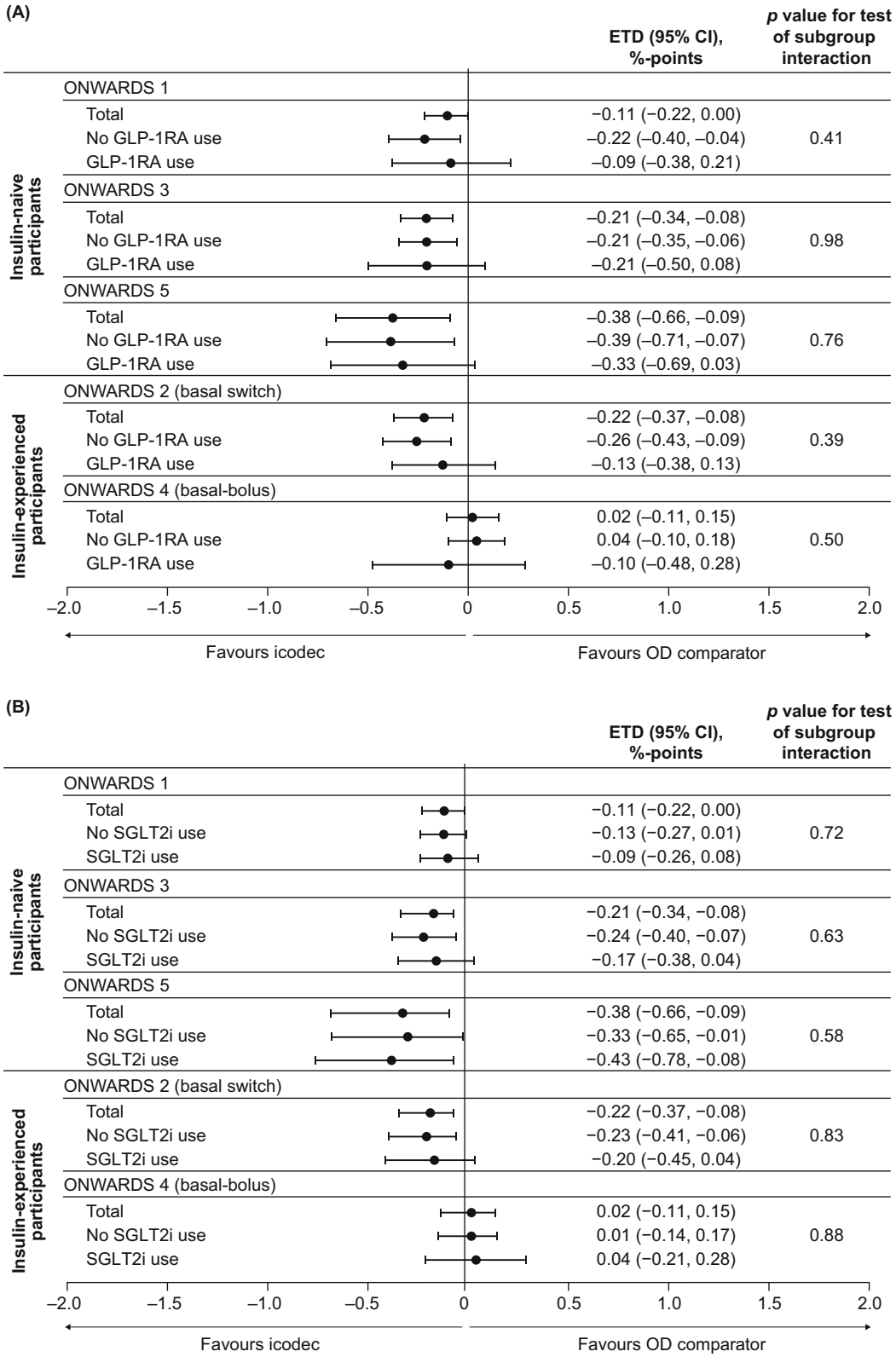

FIGURE 1 ETD in HbA1c (%-points) from baseline to planned EOT by baseline GLP-1RA (A) and SGLT2i (B) use. Participants were not stratified according to their baseline medication upon randomization. OD comparators: ONWARDS 1 and 4, glargine U100; ONWARDS 2 and 3, degludec; ONWARDS 5, degludec, glargine U100 or glargine U300. EOT visit: ONWARDS 1, week 78; ONWARDS 2–4, week 26; ONWARDS 5, week 52. CI, confidence interval; degludec, insulin degludec; EOT, end of treatment; ETD, estimated treatment difference; glargine U100, insulin glargine U100; glargine U300, insulin glargine U300; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; icodec, insulin icodec; OD, once-daily; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

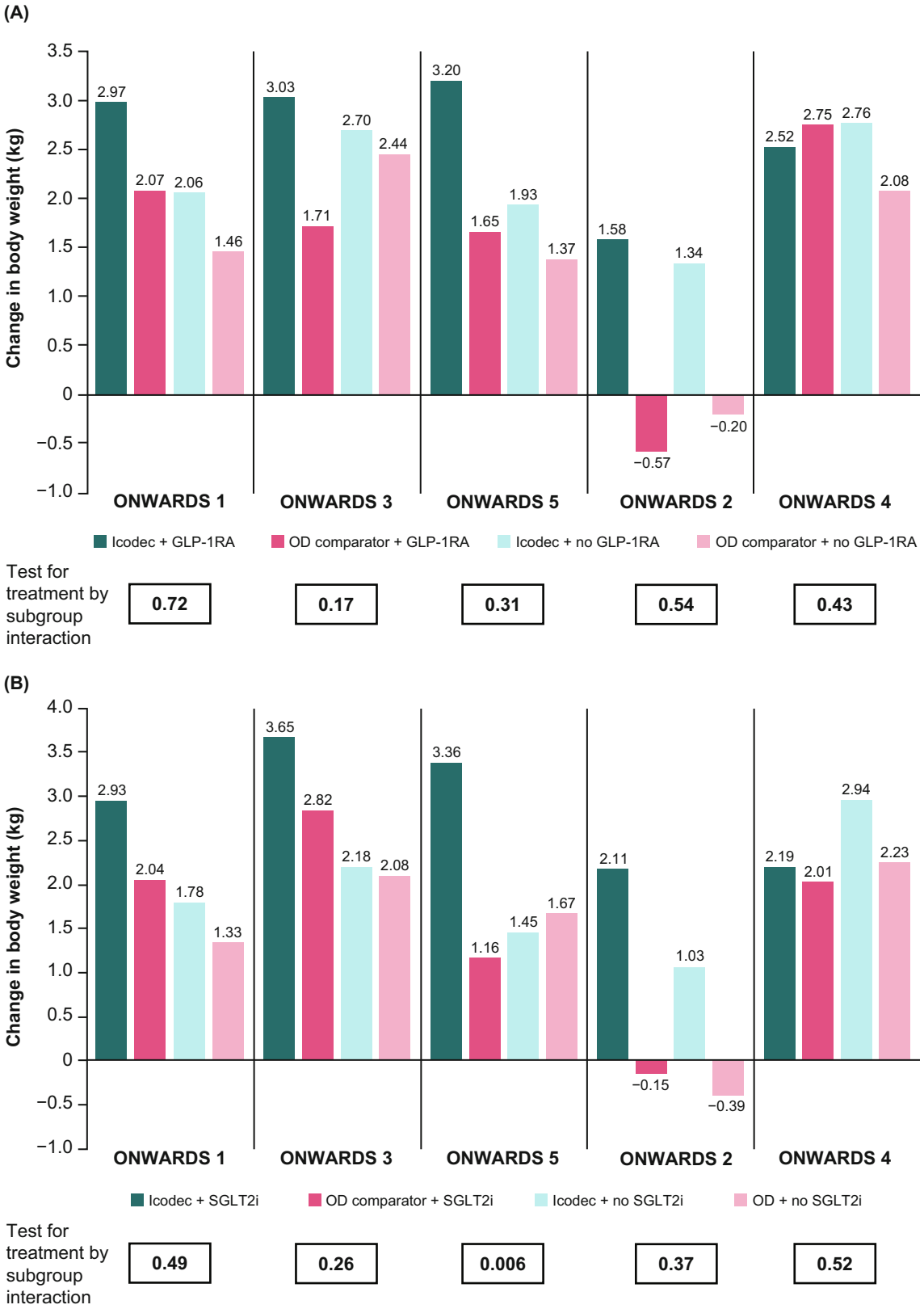

FIGURE 2 Estimated mean change in body weight from baseline to planned EOT by baseline GLP-1RA (A) and SGLT2i (B) use. Participants were not stratified according to their baseline medication upon randomization. OD comparators: ONWARDS 1 and 4, glargine U100; ONWARDS 2 and 3, degludec; ONWARDS 5, degludec, glargine U100 or glargine U300. EOT visit: ONWARDS 1, week 78; ONWARDS 2–4, week 26; ONWARDS 5, week 52. degludec, insulin degludec; EOT, end of treatment; glargine U100, insulin glargine U100; glargine U300, insulin glargine U300; GLP-1RA, glucagon-like peptide-1 receptor agonist; icodec, insulin icodec; OD, once-daily; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

TABLE 1 Mean weekly basal insulin dose during the last 2 weeks of treatment according to baseline GLP-1RA or SGLT2i use.

	LS mean basal insulin dose, U/week (95% CI) [U/day]				
	With GLP-1RA/SGLT2i use at baseline		Without GLP-1RA/SGLT2i use at baseline		*p* value for test of subgroup interaction
Trial	Icodec	OD comparator	Icodec	OD comparator	
GLP-1RA analysis					
ONWARDS 1 (insulin-naive)	244 (209, 285) [35]	235 (203, 272) [34]	220 (205, 236) [31]	234 (218, 251) [33]	0.40
ONWARDS 3 (insulin-naive)	219 (184, 260) [31]	195 (161, 236) [28]	200 (184, 218) [29]	185 (170, 201) [26]	0.79
ONWARDS 5 (insulin-naive)	264 (236, 295) [38]	204 (183, 227) [29]	214 (200, 229) [31]	178 (166, 191) [25]	0.42
ONWARDS 2 (basal switch; insulin-experienced)	278 (247, 313) [40]	260 (232, 292) [37]	265 (247, 284) [38]	239 (223, 256) [34]	0.70
ONWARDS 4 (basal-bolus; insulin-experienced)	334 (285, 392) [48]	291 (247, 344) [42]	301 (284, 320) [43]	278 (262, 295) [40]	0.65
SGLT2i analysis					
ONWARDS 1 (insulin-naive)	228 (206, 253) [33]	255 (229, 283) [36]	221 (204, 240) [32]	224 (207, 242) [32]	0.31
ONWARDS 3 (insulin-naive)	212 (188, 239) [30]	187 (163, 213) [27]	199 (181, 220) [28]	186 (170, 204) [27]	0.61
ONWARDS 5 (insulin-naive)	235 (215, 257) [34]	173 (158, 189) [25]	220 (203, 238) [31]	196 (181, 212) [28]	0.03
ONWARDS 2 (basal switch; insulin-experienced)	292 (263, 324) [42]	249 (224, 277) [36]	256 (238, 276) [37]	242 (225, 260) [35]	0.28
ONWARDS 4 (basal-bolus; insulin-experienced)	307 (277, 341) [44]	279 (252, 308) [40]	304 (285, 325) [43]	280 (262, 299) [40]	0.88

Note: OD comparators: ONWARDS 1 and 4, glargine U100; ONWARDS 2 and 3, degludec; ONWARDS 5, degludec, glargine U100 or glargine U300. EOT visit: ONWARDS 1, week 78; ONWARDS 2–4, week 26; ONWARDS 5, week 52.
Abbreviations: CI, confidence interval; degludec, insulin degludec; EOT, end of treatment; glargine U100, insulin glargine U100; glargine U300, insulin glargine U300; GLP-1RA, glucagon-like peptide-1 receptor agonist; icodec, insulin icodec; LS, least-squares; OD, once-daily; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

TABLE 2 Observed rates of clinically significant or severe hypoglycaemia (events/PYE) according to baseline GLP-1RA or SGLT2i use.

	Observed rates of clinically significant or severe hypoglycaemia, events/PYE							
	With GLP-1RA use at baseline		Without GLP-1RA use at baseline		With SGLT2i use at baseline		Without SGLT2i use at baseline	
Trial	Icodec	OD comparator	Icodec	OD comparator	Icodec	OD comparator	Icodec	OD comparator
ONWARDS 1 (insulin-naive)	0.17	0.09	0.32	0.17	0.29	0.15	0.30	0.16
ONWARDS 3 (insulin-naive)	0.24	0.14	0.33	0.15	0.13	0.11	0.44	0.16
ONWARDS 5 (insulin-naive)	0.11	0.07	0.22	0.17	0.13	0.07	0.23	0.21
ONWARDS 2 (basal switch; insulin-experienced)	0.27	0.10	0.89	0.34	0.38	0.27	0.91	0.28
ONWARDS 4 (basal-bolus; insulin-experienced)	5.65	3.12	5.64	5.96	3.21	4.34	6.59	6.18

Note: Clinically significant hypoglycaemia (level 2): blood glucose value of <54 mg/dL (3.0 mmol/L) confirmed by blood glucose meter. Severe hypoglycaemia (level 3): hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery. OD comparators: ONWARDS 1 and 4, glargine U100; ONWARDS 2 and 3, degludec; ONWARDS 5, degludec, glargine U100 or glargine U300.
Abbreviations: degludec, insulin degludec; glargine U100, insulin glargine U100; glargine U300, insulin glargine U300; GLP-1RA, glucagon-like peptide-1 receptor agonist; icodec, insulin icodec; PYE, patient-year of exposure; OD, once-daily; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

3.4 | Hypoglycaemia

Overall, the rates of clinically significant or severe hypoglycaemia were very low across treatment arms irrespective of GLP-1RA or SGLT2i use at baseline in ONWARDS 1, 2, 3 and 5 (<1 episode/PYE) (Table 2). As expected, higher numbers of clinically significant or severe hypoglycaemic episodes were observed across subgroups and treatment arms in ONWARDS 4 (basal-bolus trial) than in the other

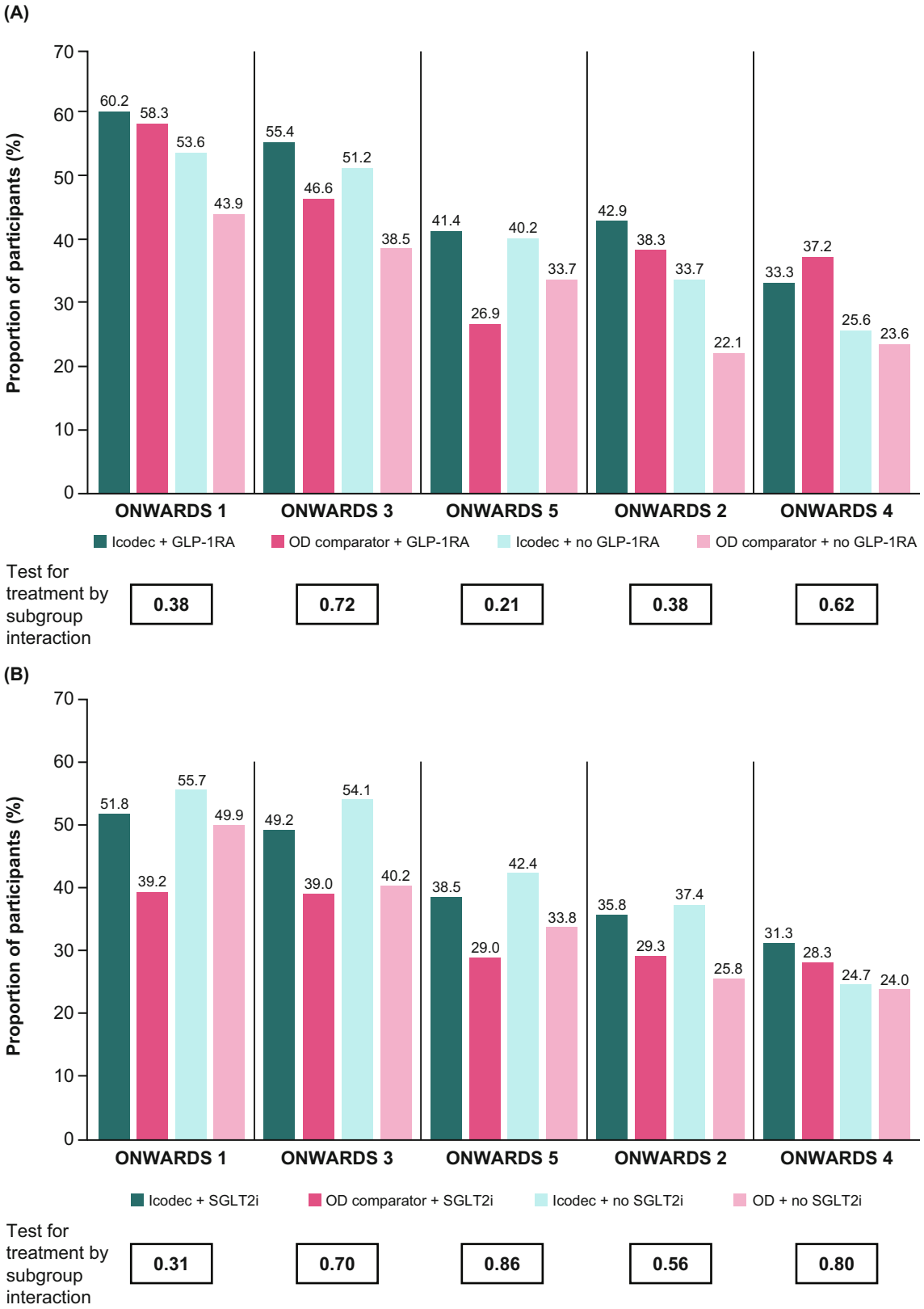

FIGURE 3 Legend on next page.

ONWARDS trials; among GLP-1RA users, the rates were numerically higher in the icodec arm (5.65 events/PYE) than in the comparator arm (3.12 events/PYE). However, the rate of clinically significant or severe hypoglycaemia among non-users was similar in the icodec arm (5.64 events/PYE) and the comparator arm (5.96 events/PYE). SGLT2i users in ONWARDS 4 had a numerically lower rate of clinically significant or severe hypoglycaemia than non-users across treatment arms.

3.5 | Composite assessment

In ONWARDS 1, 2, 3 and 5, the proportion of participants who achieved an HbA1c below 7% (53 mmol/mol) at EOT without clinically significant or severe hypoglycaemic episodes in the previous 12 weeks was numerically higher with icodec versus comparators, regardless of baseline GLP-1RA status (Figure 3A). A similar trend was observed across all five trials when analysing by baseline SGLT2i status (Figure 3B). In ONWARDS 4, a numerically higher proportion of GLP-1RA users in the comparator arm (37.2%) achieved HbA1c below 7% (53 mmol/mol) at EOT without clinically significant or severe hypoglycaemic episodes compared with GLP-1RA users in the icodec arm (33.3%). Overall, there was no statistically significant treatment by GLP-1RA or SGLT2i subgroup interaction for the composite assessment in any trial ($p > 0.05$ across trials).

4 | DISCUSSION

This post hoc analysis of ONWARDS 1–5 demonstrated that icodec had a favourable efficacy profile and comparable hypoglycaemia profile versus once-daily comparators in adults with T2D regardless of GLP-1RA and/or SGLT2i use at baseline. Individuals with long-standing T2D commonly require more than one glucose-lowering therapy to achieve glycaemic targets.[1,14] GLP-1RAs or SGLT2is are recommended therapy options for individuals with T2D who have comorbid cardiovascular and/or kidney disease or have risk factors for said diseases.[4] In the ONWARDS 1–5 trials, between 12.7% and 27.3% of participants in the icodec arm were treated with GLP-1RAs at baseline, and between 28.2% and 43.2% of participants in the icodec arm were treated with SGLT2is at baseline. Therefore, determining the treatment effect of adding icodec to stable GLP-1RA or SGLT2i therapy was warranted.

Previous studies have demonstrated that treatment of individuals with T2D with a once-daily basal insulin analogue in combination with a GLP-1RA or SGLT2i significantly reduces HbA1c compared with treatment with basal insulin alone.[15–19] Analysis of the change in HbA1c from baseline to EOT in this analysis demonstrated that there were no statistically significant treatment by GLP-1RA or SGLT2i subgroup interactions in HbA1c changes, indicating that icodec adequately improved HbA1c in participants across all five trials, regardless of background GLP-1RA and/or SGLT2i use.

The differing baseline characteristics of participants who received GLP-1RA and/or SGLT2i at screening compared with those who did not were confounding factors in this study. Indeed, the mean body weight of GLP-1RA users at baseline was numerically higher than that of non-users (between 3.0 kg and 14.0 kg difference in users vs. non-users across the trials). This was an expected finding in alignment with ADA guidelines, which recommend GLP-1RAs as a first-line pharmacological therapy for T2D in individuals with overweight or obesity.[3] Across treatment arms, participants who were treated with both a GLP-1RA and an SGLT2i generally had a higher BMI (all trials) and a longer diabetes duration (ONWARDS 1, 3, 4, 5) at baseline than the total treatment arm populations.[7–11] The estimated change in mean body weight from baseline to EOT was generally numerically higher in the icodec arm versus the comparator arm regardless of GLP-1RA or SGLT2i use, and, except for SGLT2i users versus non-users in ONWARDS 5, there were no statistically significant treatment by GLP-1RA or SGLT2i subgroup interactions in body weight changes. The modest changes in mean body weight from baseline to EOT with icodec treatment (≤3.7 kg across subgroups and trials) were consistent with the expected side effects of treatment with an insulin analogue, and treatment differences between arms were small irrespective of background GLP-1RA and/or SGLT2i use (≤2.3 kg across trials). The relative change in mean body weight from baseline to EOT was minor and similar across trials and treatment arms (by −1% to +4%), and treatment ratios between arms were similar across trials irrespective of GLP-1RA use (1.00 to 1.02). This finding suggests that the results observed for change in mean body weight from baseline to EOT in GLP-1RA users versus non-users were influenced by the imbalances in baseline mean body weight observed between groups, thus resulting in GLP-1RA users with a higher baseline body weight tending to gain more absolute weight compared with non-users.

Although GLP-1RA and SGLT2i users generally received numerically higher weekly basal insulin doses during the last 2 weeks of treatment than non-users, it was noted that the rates of clinically significant or severe hypoglycaemia were overall numerically lower among GLP-1RA and SGLT2i users than non-users across both treatment arms in ONWARDS 1, 2, 3 and 5. Although this may have been

FIGURE 3 Estimated proportion of participants who achieved an HbA1c under 7% (53.0 mmol/mol) at EOT without clinically significant or severe hypoglycaemic episodes in the previous 12 weeks by baseline GLP-1RA (A) and SGLT2i (B) use. Participants were not stratified according to their baseline medication upon randomization. OD comparators: ONWARDS 1 and 4, glargine U100; ONWARDS 2 and 3, degludec; ONWARDS 5, degludec, glargine U100 or glargine U300. EOT visit: ONWARDS 1, week 78; ONWARDS 2–4, week 26; ONWARDS 5, week 52. degludec, insulin degludec; EOT, end of treatment; glargine U100, insulin glargine U100; glargine U300, insulin glargine U300; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; icodec, insulin icodec; OD, once-daily; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

due to confounding factors that were unaccounted for in the analysis, other possible reasons for this observation in GLP-1RA users include the physiological effects of GLP-1RAs on glucagon secretion, insulin production and/or glycaemic variability in individuals with T2D.[20–22] The higher baseline body weight of GLP-1RA users than non-users observed across ONWARDS trials may also have contributed to this finding because participants with higher body weight likely require higher basal insulin doses and may have an increased resistance to insulin, meaning they were therefore less likely to experience insulin-induced hypoglycaemia. Possible increased glucagon secretion following SGLT2i therapy and a low glycaemic variability among SGLT2i users may also explain the lower rates of hypoglycaemia in SGLT2i users than in non-users;[23,24] however, evidence for this hypothesis is limited in individuals with T2D. Although the mean weekly basal insulin dose during the last 2 weeks of treatment was numerically higher in the icodec arm than in the comparator arm irrespective of GLP-1RA or SGLT2i use, the treatment difference between arms was generally low (1–3 U/day in most comparisons).

As expected in individuals receiving basal-bolus insulin injections, the rate of clinically significant or severe hypoglycaemia was higher across treatment arms in ONWARDS 4 than in the other trials. However, the rate of clinically significant or severe hypoglycaemia observed across GLP-1RA subgroups in the icodec arm of ONWARDS 4 was consistent with the rate observed across the total ONWARDS 4 participant population (5.6 episodes/PYE).[10] The rate of clinically significant or severe hypoglycaemia was less than one episode/PYE across baseline treatment subgroups and treatment arms in ONWARDS 1, 2, 3 and 5, a finding consistent with those observed in the whole trial population from these trials.[7–9,11] Overall, these findings suggest that the risk of hypoglycaemia with icodec treatment is low, irrespective of GLP-1RA and/or SGLT2i use or non-use.

Except for GLP-1RA users in ONWARDS 4, a numerically higher proportion of participants in the icodec arm compared with the comparator arm achieved the composite assessment of achievement of an HbA1c under 7% (53 mmol/mol) without clinically significant or severe hypoglycaemic episodes, regardless of baseline medication subgroup. The reason for this discrepancy may be attributable to ONWARDS 4 having a smaller difference between treatment arms in the overall trial population and a lower number and proportion of participants who received GLP-1RAs at baseline than the other ONWARDS trials.

A key strength of this study is that it is the first analysis to demonstrate the effect of adding a once-weekly basal insulin to stable GLP-1RA and/or SGLT2i therapy in individuals with T2D. The large, multinational cohort of participants with T2D ($n = 3765$) assessed in this post hoc analysis additionally strengthens the general applicability of the ONWARDS programme findings across different populations of individuals with T2D worldwide. A limitation of this study is that participants were not randomized to use GLP-1RA and/or SGLT2i medication; therefore, this variable was not controlled for as part of the trial design. Because individuals with T2D initiate a non-insulin glucose-lowering therapy for specific reasons (e.g. body weight, comorbidities, insulin sensitivity, duration of disease, cost or treatment availability),[1] this will have inevitably introduced bias into the analysis. Furthermore, the analysis did not account for participants who discontinued background therapy during the studies. However, the number of participants who discontinued background GLP-1RA and/or SGLT2i therapy was low across trials and was expected to have a minimal effect on the overall findings of the study. Finally, the previously noted differences in trial design and populations between the five ONWARDS trials precluded a meta-analysis of the data by GLP-1RA and/or SGLT2i use.

Overall, across GLP-1RA and SGLT2i subgroups, there were no statistically significant treatment by baseline medication subgroup interaction effects with respect to: change in HbA1c from baseline to EOT; change in body weight from baseline to EOT (except for SGLT2i use in ONWARDS 5); mean weekly basal insulin dose during the last 2 weeks of treatment (except for SGLT2i use in ONWARDS 5); and achievement of the composite assessment. The rates of clinically significant or severe hypoglycaemia were low across the treatment arms of ONWARDS 1, 2, 3 and 5. Overall, this analysis demonstrated that the efficacy and hypoglycaemia profile of once-weekly icodec versus once-daily comparators was generally consistent among adults with T2D across ONWARDS trials, irrespective of GLP-1RA or SGLT2i treatment at baseline. These results provide evidence to suggest that no alterations to GLP-1RA and/or SGLT2i treatment are required in individuals with T2D who are initiating icodec therapy. However, it should be noted that adjustments to background therapy and/or icodec dose in some individuals may be required owing to the individualized nature of insulin dosing.

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

Tina Vilsbøll has served on scientific advisory panels, been part of speaker's bureaus, served as a consultant to and/or received research support from Amgen, AstraZeneca, Boehringer Ingelheim, Carmot/Roche, Eli Lilly, Gilead, GSK, Mundipharma, Novo Nordisk, Sanofi, Sun Pharmaceuticals and Zealand Pharma. Ariel Fu and Stinne Byrholdt Søgaard are employees of Novo Nordisk and hold stock in Novo Nordisk. Monika Kellerer has received consulting fees from Abbott, Bayer AG, Boehringer Ingelheim, Eli Lilly, MSD, Novo Nordisk and Sanofi and honoraria for lectures, presentations, speakers' bureaus and

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PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16328.

DATA AVAILABILITY STATEMENT

Individual participant data will be shared in data sets in a de-identified/anonymized format. Shared data will include data sets from clinical research sponsored by Novo Nordisk that was completed after 2001 for product indications approved in both the European Union and the USA. The study protocol and the redacted clinical study report will be made available according to Novo Nordisk's data sharing commitments. These data will be available permanently after research completion and approval of product and product use in both the European Union and the USA (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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