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Benefits of insulin degludec/liraglutide are maintained even in patients discontinuing sulphonylureas or dipeptidyl peptidase-4 inhibitors upon initiation of degludec/liraglutide therapy: A post hoc analysis of the DUAL II and DUAL IX trials

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Abstract

Aim: To investigate the efficacy and safety of initiating insulin degludec/liraglutide (IDegLira) in patients with type 2 diabetes (T2D) who had discontinued pretrial sulphonylureas (SUs) or dipeptidyl peptidase-4 inhibitors (DPP4is) versus patients not previously treated with these regimens.

Materials and Methods: In DUAL II, patients with T2D uncontrolled on basal insulin and metformin ± SU/glinides were randomized to insulin degludec or IDegLira (both capped at 50 U). In DUAL IX, patients were randomized to insulin glargine U100 (no maximum dose) or IDegLira, as add-on to sodium-glucose co-transporter-2 inhibitors ± oral antidiabetic drugs. In this post hoc analysis, patients were grouped according to pretrial use of SU (DUAL II) or DPP4i (DUAL IX).

Results: Regardless of pretrial SU/DPP4i use, IDegLira was favourable versus insulin comparators with respect to change in HbA1c and body weight. Lower hypoglycaemia rates and comparable end-of-trial daily insulin dose were achieved with IDegLira, regardless of pretrial regimen. There was no clinically relevant increase in mean self-measured blood glucose in the early weeks after IDegLira initiation. There was no statistically significant interaction between the randomized treatments and previous SU/DPP4i use.

Conclusions: IDegLira was more favourable compared with degludec or glargine U100 in terms of change in HbA1c and body weight, regardless of antecedent treatment. Clinicians should be aware of a potential transient rise in self-measured blood glucose when transitioning therapy in patients. This shows that SUs/DPP4is can be safely discontinued, without deterioration in glycaemic control when initiating IDegLira, allowing a simplified treatment regimen.

KEYWORDS

glucagon-like peptide-1 analogue, insulin therapy, liraglutide, randomized trial, type 2 diabetes.

1 | INTRODUCTION

The progressive nature of type 2 diabetes (T2D) often requires treatment intensification to optimally control blood glucose levels and thereby help to avoid long-term diabetes-related complications. It can be challenging for clinicians to know how to make adjustments when patients move from oral to injectable therapy.[1,2] The reasons for this include concerns about increasing the risk of hypoglycaemia if an agent is added, or fear of failure to maintain glycaemic control if an agent is discontinued. In clinical practice, there is a tendency for clinicians to keep adding agents onto a regimen, without discontinuing any prior treatment, even if it no longer provides benefit to the patient.[3,4] For example, the use of sulphonylureas (SUs) and insulin are each associated with a risk of hypoglycaemia,[2] which has been linked to increased mortality rates,[5] and when these agents are used together, the risk of hypoglycaemia is further increased.[6] A retrospective study revealed that more than 20% of patients with diabetes are often overtreated, and this practice is particularly common in elderly patients.[4,7-9]

Although the latest guidelines provide extensive guidance on when and how best to intensify treatment, recommendations on simplifying treatment regimens are starting to emerge. The use of simpler regimens such as fixed-ratio combination therapies including degludec/liraglutide (IDegLira) has recently been advocated, particularly among older adults with T2D and a history of cognitive impairment.[10,11] These guidelines emphasize the need for simplified outpatient diabetes medication regimens that minimize the risk of hypoglycaemia, for example by avoiding SUs, to improve compliance and prevent treatment-related complications.[10] The impact of discontinuing prior agents requires further investigation, to help clinicians reduce treatment burden and complexity in patients, while avoiding loss of glycaemic control.

IDegLira is a fixed-ratio combination of basal insulin degludec 100 units/mL (degludec) and the glucagon-like peptide-1 receptor agonist (GLP-1RA) liraglutide (3.6 mg/mL) that is administered as a simple once-daily injection.[12] The safety and efficacy of IDegLira were investigated in the Dual Action of Liraglutide and Insulin Degludec in Type 2 Diabetes (DUAL) clinical trial programme.[13-20]

The DUAL II and DUAL IX trials assessed the safety and efficacy of IDegLira in patients with T2D treated with oral antidiabetic drug (OAD) therapy or basal insulin (DUAL II). The DUAL II trial established the distinct contribution of the liraglutide component of IDegLira by comparing IDegLira with degludec, both capped at 50 U,[14] and the DUAL IX trial investigated IDegLira versus insulin glargine 100 units/mL (IGlar U100) added on to sodium-glucose co-transport protein-2 inhibitors (SGLT2is).[20] Patients discontinued SUs in DUAL II[14] or dipeptidyl peptidase-4 inhibitors (DPP4is) in DUAL IX[20] before starting IDegLira. The results from the DUAL II and DUAL IX trials showed IDegLira to have a favourable safety and efficacy profile, including superior HbA1c lowering and a lower risk of hypoglycaemia and weight gain, compared with degludec[14] and IGlar U100,[20] respectively.

This post hoc analysis investigated glycaemic control and other efficacy and safety endpoints in patients discontinuing pretrial SUs (DUAL II) or DPP4is (DUAL IX). This allows us to further examine if IDegLira permits patients to achieve treatment targets with a simpler treatment regimen and can help to inform clinical decision-making when intensifying antidiabetes therapies.

2 | MATERIALS AND METHODS

This was a post hoc analysis of the DUAL II (NCT01392573)[14] and DUAL IX (NCT02773368)[20] trials, which have been described in full in their respective primary reports.[14,20] Both trials were phase III, randomized (1:1), multinational, multicentre, treat-to-target trials, with a 26-week treatment duration. DUAL II was a double-blind trial and DUAL IX was open-label.

The DUAL II trial compared the efficacy and safety of once-daily IDegLira + metformin with degludec + metformin in patients who were receiving basal insulin and metformin with or without SUs/glinides. The DUAL IX trial investigated the efficacy and safety of IDegLira compared with IGlar U100 as an add-on treatment to SGLT2is, with or without other OADs in insulin-naïve adult patients. Existing SU (in DUAL II) and DPP4i (in DUAL IX) therapies were discontinued at randomization.

This post hoc analysis compared the results of patients discontinuing pretrial SUs (DUAL II) or DPP4is (DUAL IX) (pretrial OAD), with those of patients not previously treated with these agents when initiating IDegLira. In the DUAL II trial, patients were grouped by previous treatment with SUs (SU group or non-SU group). If patients were previously treated with SUs (SU group), SUs/glinides were discontinued at randomization, and the use of metformin was continued at the pretrial dose throughout the 26-week treatment period. IDegLira was administered at a starting dose of 16 units (U) (16 U degludec/0.6 mg liraglutide) with a maximum allowed dose of 50 U (50 U degludec/1.8 mg liraglutide). IDegLira was titrated twice-weekly according to a predefined titration algorithm based on the mean of three preceding, consecutive, fasting self-measured blood glucose (SMBG) values, with a prebreakfast SMBG target of between 4.0–-5.0 mmol/L (72–90 mg/dL). Degludec was initiated at 16 U titrated twice-weekly, with a maximum allowed dose of 50 U.

In this post hoc analysis of the DUAL IX trial, patients were grouped by pretrial OAD treatment (DPP4i group or non-DPP4i group). If patients were previously treated with DPP4is, DPP4is were discontinued at randomization and SGLT2is and all other OADs were continued at pretrial doses throughout the 26-week treatment period. IDegLira was administered at a starting dose of 10 U (10 U degludec/0.36 mg liraglutide) with a maximum allowed dose of 50 U (50 U degludec/1.8 mg liraglutide). IDegLira was titrated twice-weekly in the same manner as described for DUAL II above. IGlar U100 was administered at the recommended starting dose of 10 U, titrated twice-weekly, with no maximum dose.

Both trials were performed in accordance with the Declaration of Helsinki[21] and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice.[22]

The primary endpoint for both trials was change from baseline in HbA1c after 26 weeks. In addition, the following secondary endpoints

were also assessed in this post hoc study, according to antecedent treatment: change in body weight, SMBG, fasting plasma glucose (FPG), end-of-trial (EOT) daily insulin dose and the number of confirmed hypoglycaemic episodes per patient-year of exposure (PYE). In DUAL II, the analysed hypoglycaemic events were either episodes confirmed by a plasma glucose level of <3.1 mmol/L (56 mg/dL), regardless of symptoms or severe episodes requiring the assistance of another person. In DUAL IX, the analysed hypoglycaemic events consisted of either blood glucose-confirmed symptomatic events (with symptoms consistent with hypoglycaemia) or severe episodes requiring the assistance of another person.

2.1 | Statistical analysis

In DUAL II, changes from baseline in HbA1c, FPG, body weight and EOT insulin dose after 26 weeks of treatment were analysed with an ANCOVA model with: region; pretrial use of SUs at screening; randomized treatment and interaction between pretrial use of SUs and randomized treatment as fixed factors; and baseline value as covariate (and baseline HbA1c for insulin dose). Missing data were imputed using last observation carried forward. The number of treatment-emergent hypoglycaemic episodes was analyzed using a negative binomial regression model with a log link, and the logarithm of the time period in which a hypoglycaemic episode is considered treatment-emergent at offset; and the same fixed factors as the ANCOVA model.

In the DUAL IX trial, the estimands framework was used. The primary estimand was the difference at 26 weeks between patients with T2D randomized to IDegLira or IGlar U100, both in combination with SGLT2is ± OADs, regardless of whether patients remained on initially assigned treatment. Missing data were imputed by unconditional reference-based multiple imputation, including data obtained after premature treatment discontinuation. The post hoc analysis for the DUAL IX trial was performed using the same multiple imputation approach addressing the primary estimand. For continuous endpoints, the response and change from baseline in response after 26 weeks were analysed using an ANCOVA model with treatment, pretrial use of DPP4is, region and interaction between treatment and pretrial DPP4i as factors, and corresponding baseline value as covariate (baseline HbA1c for insulin dose). The number of treatment-emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes was analysed using a negative binomial regression model with a log link and the logarithm of the exposure time as offset. The model included treatment, pretrial DPP4i use and interaction between treatment and pretrial DPP4i use, as fixed factors.

3 | RESULTS

3.1 | Patients

The number of patients in each subgroup is shown in Table 1. Patients' baseline characteristics were broadly similar between patients in the SU and non-SU groups (DUAL II)[14] (Table 1, Table S1) and patients in the DPP4i and non-DPP4i groups (DUAL IX)[20] (Table 1). However, in both trials, mean duration of diabetes at screening was higher in the subgroups discontinuing pretrial OADs: 11.5 and 9.8 years for SU and non-SU groups, respectively, and 11.5 and 8.6 years in the DPP4i and non-DPP4i groups, respectively.

3.2 | HbA1c

In both trials, HbA1c improved in both treatment arms, but to a statistically significant greater extent with IDegLira ($P < 0.0001$).[14,20] Greater improvement in HbA1c with IDegLira compared with insulin comparator was seen irrespective of whether OADs were discontinued at randomization (Figure 1). Of note, in the short term, at weeks 4 and 12, there was no clinically significant worsening in HbA1c when pretrial OADs were stopped and patients were transitioned to an injectable therapy (Table S2).

In the DUAL II trial, the estimated treatment difference (ETD) for HbA1c at EOT in the SU group was −12.31 mmol/mol (−15.46; −9.15)$_{95\%\ \text{confidence interval (CI)}}$ (−1.13% [−1.41; −0.84]$_{95\%\ \text{CI}}$), and −10.32 mmol/mol (−13.49; −7.16)$_{95\%\ \text{CI}}$ (−0.94% [−1.23; −0.66]$_{95\%\ \text{CI}}$) in the non-SU group (Table 2). In the DUAL IX trial, the ETDs were reported to be −4.33 mmol/mol (−7.05; −1.62)$_{95\%\ \text{CI}}$ (−0.40% [−0.64; −0.15]$_{95\%\ \text{CI}}$) and − 3.69 mmol/mol (−5.58; −1.80)$_{95\%\ \text{CI}}$ (−0.34% [−0.51, −0.16]$_{95\%\ \text{CI}}$) in the DPP4i and non-DPP4i groups, respectively (Table 3). Overall, the treatment effect on mean change in HbA1c was consistent between pretrial OAD groups in both trials, with no statistically significant interaction between the randomized treatment and previous SU ($P = 0.3828$) or DPP4i use ($P = 0.7030$).

3.3 | Body weight

IDegLira was associated with more favourable outcomes in terms of body weight compared with degludec in DUAL II and IGlar U100 in DUAL IX, regardless of antecedent treatment (Tables 2 and 3). After 26 weeks in the DUAL II trial, IDegLira treatment led to reductions in mean body weight for both the SU and non-SU groups. The ETDs were reported to be −2.77 kg (−3.75; −1.79)$_{95\%\ \text{CI}}$ and −2.41 kg (−3.39; −1.43)$_{95\%\ \text{CI}}$ in the SU and non-SU groups, respectively (Table 2). In the DUAL IX trial, the ETDs were reported to be −1.84 kg (−3.11; −0.56)$_{95\%\ \text{CI}}$ and −1.95 kg (−2.83; −1.08)$_{95\%\ \text{CI}}$ in the DPP4i and non-DPP4i groups, respectively (Table 3). Overall, the treatment effect on mean change in body weight was consistent between pretrial OAD groups in both trials, with no statistically significant interaction between the randomized treatment and previous SU ($P = 0.6137$) or DPP4i ($P = 0.8858$) use.

3.4 | Hypoglycaemia

In alignment with the overall trial results from DUAL II, the rates of hypoglycaemia in the IDegLira arm were lower than in the degludec arm, regardless of antecedent treatment. Estimated rate ratios (ERRs)

TABLE 1 Baseline characteristics

	DUAL II				DUAL IX			
	SU group		Non-SU group		DPP4i group		Non-DPP4i group	
	IDegLira	Degludec	IDegLira	Degludec	IDegLira	IGlar U100	IDegLira	IGlar U100
N	99	99	100	100	65	71	145	139
Duration of diabetes, years	11.34 (6.21)	11.57 (6.95)	9.27 (5.64)	10.25 (7.10)	12.28 (6.12)	10.75 (6.56)	8.69 (5.93)	8.57 (6.07)
HbA1c, mmol/mol	72.12 (8.15)	73.25 (7.28)	72.15 (8.15)	73.14 (8.59)	66.08 (9.69)	65.96 (9.92)	66.15 (10.41)	68.93 (12.58)
%	8.75 (0.75)	8.85 (0.67)	8.75 (0.75)	8.84 (0.79)	8.20 (0.89)	8.18 (0.91)	8.20 (0.95)	8.46 (1.15)
Body weight, kg	96.50 (22.81)	93.92 (20.25)	94.26 (15.43)	93.15 (19.79)	88.63 (19.09)	84.51 (16.89)	89.53 (16.99)	88.60 (17.31)
FPG, mmol/L	9.51 (2.83)	9.64 (2.55)	9.87 (3.01)	9.47 (3.57)	9.60 (2.58)	9.56 (2.24)	9.46 (2.74)	9.57 (2.49)
mg/dL	171.37 (51.07)	173.77 (45.91)	177.76 (54.19)	170.54 (64.28)	172.94 (46.41)	172.32 (40.40)	170.54 (49.41)	172.53 (44.81)
Daily insulin dose, U[†]	27.5 (7.0)	26.8 (7.1)	30.6 (8.1)	31.5 (7.5)	10.99 (0.95)	11.29 (1.89)	11.18 (1.47)	10.99 (0.87)

Abbreviations: Degludec, insulin degludec; DPP4i, dipeptidyl peptidase-4 inhibitor; FPG, fasting plasma glucose; IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine U100; SD, standard deviation; SU, sulphonylurea; U, units.

Data are mean values (SD) unless otherwise stated.

[†]Daily insulin dose was for screening in DUAL II and week 1 in DUAL IX, where patients were insulin-naïve.

for IDegLira versus degludec were 0.56 (0.26; 1.22)$_{95\%\ CI}$ and 0.88 (0.41; 1.92)$_{95\%\ CI}$, in the SU and non-SU groups, respectively (Table 2). In DUAL IX, ERRs were 0.41 (0.13; 1.29)$_{95\%\ CI}$ and 0.42 (0.22; 0.83)$_{95\%\ CI}$ in the DPP4i and non-DPP4i groups, respectively (Table 3). Overall, the treatment effect on the rates of hypoglycaemic events was consistent between pretrial OAD groups in both trials, with no statistically significant interaction between the randomized treatment and previous SU (P = 0.4221) or DPP4i (P = 0.9457) use.

3.5 | FPG

IDegLira was associated with numerically greater reductions in FPG compared with degludec in both pretrial OAD groups of DUAL II, and similar decreases to IGlar U100 in both pretrial OAD groups of DUAL IX (Figure S1). In the DUAL II trial, the ETDs were −0.94 mmol/L (−1.59; −0.30)$_{95\%\ CI}$ (−17.03 mg/dL [−28.66; −5.39]$_{95\%\ CI}$) and −0.52 mmol/L (−1.17; 0.13)$_{95\%\ CI}$ (−9.36 mg/dL [−21.05; 2.32]$_{95\%\ CI}$) in the SU and non-SU groups, respectively (Table 2). In DUAL IX, the ETDs were −0.32 mmol/L (−0.87; 0.22)$_{95\%\ CI}$ (−5.85 mg/dL [−15.74; 4.03]$_{95\%\ CI}$) and −0.33 mmol/L (−0.71; 0.05)$_{95\%\ CI}$ (−5.90 mg/dL [−12.74; 0.94]$_{95\%\ CI}$) in the DPP4i and non-DPP4i groups, respectively (Table 3). Overall, the treatment effect on mean change in FPG was consistent between pretrial OAD groups in both trials, with no statistically significant interaction between the randomized treatment and previous SU (P = 0.3618) or DPP4i (P = 0.9939) use.

3.6 | EOT total daily insulin dose

In DUAL II, mean daily insulin dose at EOT was comparable between treatment arms and pretrial OAD groups. With IDegLira, EOT daily insulin dose was 43.85 versus 45.79 U in the SU and non-SU groups, respectively. With degludec, EOT daily insulin dose was 44.87 versus 44.93 U in the SU and non-SU groups, respectively. The ETD was reported to be −0.80 U (−3.39; 1.79)$_{95\%\ CI}$ and 1.09 U (−1.52; 3.69)$_{95\%\ CI}$ in the SU and non-SU groups, respectively (Table 2). In DUAL IX, the EOT daily insulin dose was lower with IDegLira compared with IGlar U100, for both the DPP4i and non-DPP4i groups (Table 3). The ETD was reported to be −13.30 U (−20.78; −5.82)$_{95\%\ CI}$ and −16.37 U (−21.52; −11.22)$_{95\%\ CI}$ in the DPP4i and non-DPP4i groups, respectively. Overall, the treatment effect on EOT daily insulin dose was consistent between pretrial OAD groups in both trials, with no statistically significant interaction between the randomized treatment and previous SU (P = 0.3132) or DPP4i (P = 0.5083) use.

3.7 | SMBG

Overall, there was a decrease in mean SMBG in both trials irrespective of treatment arm and pretrial OAD group (Figure 2). In DUAL II, there was a nonclinically relevant increase of up to 0.4 mmol/L (7.4 mg/dL) and a clinically relevant increase of 1.3 mmol/L (22.5 mg/dL) in mean SMBG at week 1 in the SU group, in the IDegLira and degludec arms, respectively (Table S2). After week 4, an improvement in mean SMBG in both arms was observed (Table S2, Figure 2A). However, in DUAL IX there was no increase in mean SMBG in the first few weeks after initiating IDegLira at 10 U, regardless of treatment arm or antecedent treatment (Figure 2B). Patients had similar mean SMBG values at the end of the trial after receiving either IDegLira or IGlar U100.

4 | DISCUSSION

In clinical practice, DPP4is are discontinued upon GLP-1RA initiation and the dose/use of SUs are evaluated when insulin is initiated based

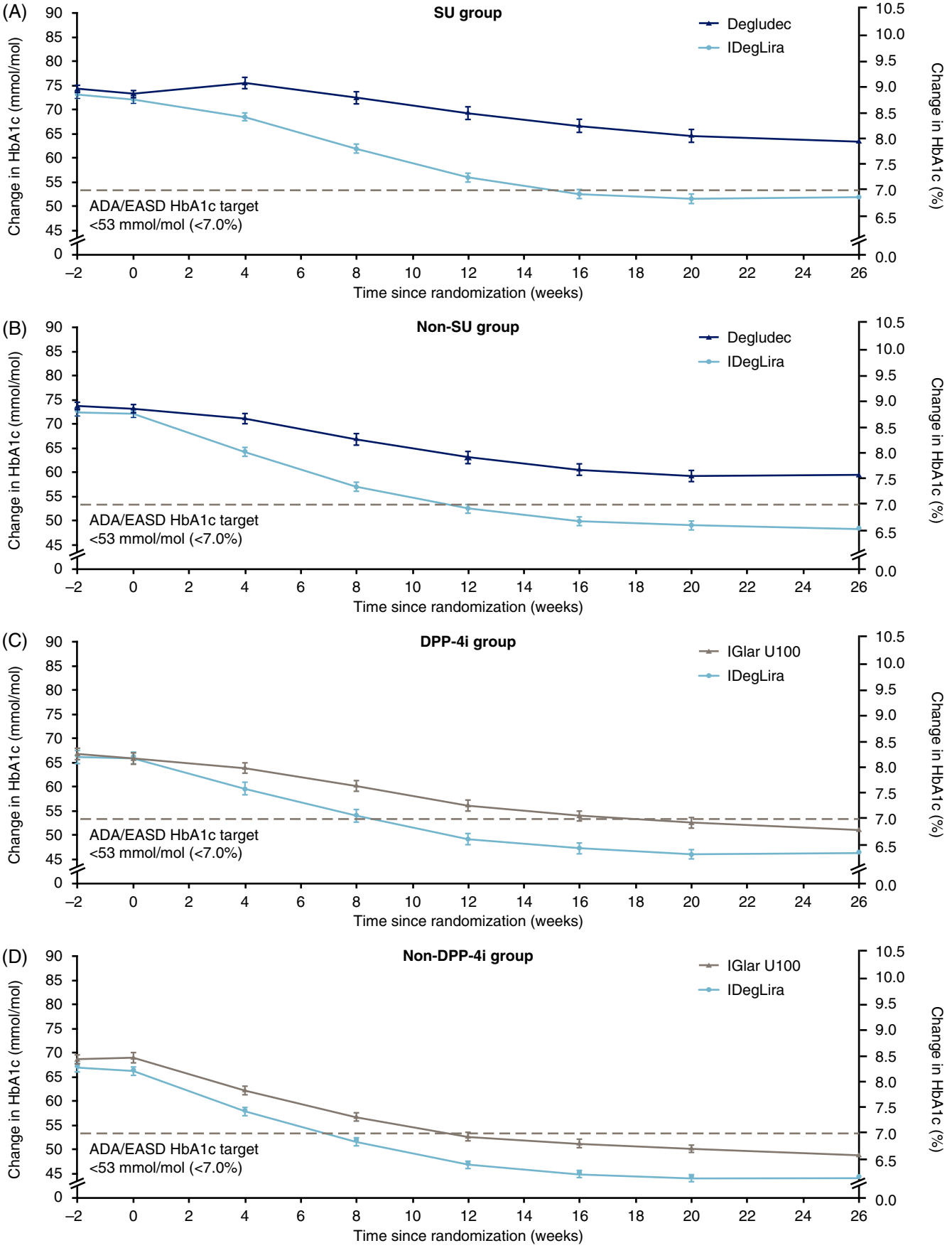

FIGURE 1 Change in mean HbA1c over 26 weeks by previous (A, B) sulphonylurea (SU) and (C, D) dipeptidyl peptidase-4 inhibitor (DPP4i) use. Data are mean (SEM) and based on the full analysis set. ADA, American Diabetes Association; Degludec, insulin degludec; EASD, European Association for the Study of Diabetes; IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine U100; SEM, standard error of the mean

TABLE 2 Outcomes after 26 weeks of treatment in DUAL II by pretrial sulphonylurea (SU) use

Category	SU group			Non-SU group			Test for treatment by subgroup interaction, *P*-value
	IDegLira (N = 99)	Degludec (N = 99)	ETD/ERR [95% CI]	IDegLira (N = 100)	Degludec (N = 100)	ETD/ERR [95% CI]	
Δ HbA1c, mmol/mol	−18.58 (13.03)	−6.83 (11.87)	ETD: −12.31 [−15.46; −9.15]	−22.91 (10.42)	−12.69 (13.19)	ETD: −10.32 [−13.49; −7.16]	0.3828
%	−1.70 (1.19)	−0.63 (1.09)	ETD: −1.13 [−1.41; −0.84]	−2.10 (0.95)	−1.16 (1.21)	ETD: −0.94 [−1.23; −0.66]	
Δ Body weight, kg	−3.06 (3.59)	−0.27 (2.64)	ETD: −2.77 [−3.75; −1.79]	−2.30 (3.75)	0.27 (3.96)	ETD: −2.41 [−3.39; −1.43]	0.6137
Δ FPG, mmol/L	−3.26 (3.15)	−2.41 (3.31)	ETD: −0.94 [−1.59; −0.30]	−3.67 (2.68)	−2.75 (3.33)	ETD: −0.52 [−1.17; 0.13]	0.3618
mg/dL	−58.75 (56.76)	−43.33 (59.57)	ETD: −17.03 [−28.66; −5.39]	−66.08 (48.24)	−49.48 (60.02)	ETD: −9.36 [−21.05; 2.32]	
End of trial daily insulin dose, U	43.85 (10.23)	44.87 (9.31)	ETD: −0.80 [−3.39; 1.79]	45.79 (8.47)	44.93 (9.74)	ETD: 1.09 [−1.52; 3.69]	0.3132
Hypoglycaemic events/PYE	1.7	3.0	ERR: 0.56 [0.26; 1.22]	1.4	2.3	ERR: 0.88 [0.41; 1.92]	0.4221
Total number of confirmed hypoglycaemic events	75	129		67	111		

Abbreviations: CI, confidence interval; Degludec, insulin degludec; ERR, estimated rate ratio; ETD, estimated treatment difference; FPG, fasting plasma glucose; IDegLira, insulin degludec/liraglutide; PYE, patient-year of exposure; SD, standard deviation; U, units.

Data are mean (SD) values unless otherwise stated. Missing data were imputed using last observation carried forward, except for hypoglycaemic events. Confirmed hypoglycaemia: patient unable to treat themselves and/or have a recorded plasma glucose of <3.1 mmol/L (56 mg/dL).

TABLE 3 Outcomes after 26 weeks of treatment in DUAL IX by pretrial dipeptidyl peptidase-4 inhibitor (DPP4i) use

Category	DPP4i group			Non-DPP4i group			Test for treatment by subgroup interaction, *P*-value
	IDegLira (N = 65)	IGlar U100 (N = 71)	ETD/ERR [95% CI]	IDegLira (N = 145)	IGlar U100 (N = 139)	ETD/ERR [95% CI]	
Δ HbA1c, mmol/mol†	−19.17 (8.67)	−15.00 (7.69)	ETD: −4.33 [−7.05; −1.62]	−22.08 (10.96)	−20.14 (12.71)	ETD: −3.69 [−5.58; −1.80]	0.7030
%†	−1.75 (−0.79)	−1.37 (0.70)	ETD: −0.40 [−0.64; −0.15]	−2.02 (1.00)	−1.84 (1.16)	ETD: −0.34 [−0.51; −0.16]	
Δ Body weight, kg†	−0.08 (3.52)	1.85 (3.60)	ETD: −1.84 [−3.11; −0.56]	0.00 (3.93)	2.07 (4.00)	ETD: −1.95 [−2.83; −1.08]	0.8858
Δ FPG, mmol/L	−3.74 (2.27)	−3.55 (2.24)	ETD: −0.32 [−0.87; 0.22]	−3.72 (3.12)	−3.48 (2.53)	ETD: −0.33 [−0.71; 0.05]	0.9939
mg/dL	−67.43 (40.92)	−64.02 (40.28)	ETD: −5.85 [−15.74; 4.03]	−66.95 (56.25)	−62.63 (45.67)	ETD: −5.90 [−12.74; 0.94]	
End of trial daily insulin dose, U†	38.72 (12.94)	52.60 (27.12)	ETD: −13.30 [−20.78; −5.82]	35.12 (13.50)	54.02 (25.68)	ETD: −16.37 [−21.52; −11.22]	0.5083
Hypoglycaemic events/ PYE	0.2	0.6	ERR: 0.41 [0.13; 1.29]	0.4	1.1	ERR: 0.42 [0.22; 0.83]	0.9457
Total number of confirmed symptomatic hypoglycaemic events	7	21		31	74		

Abbreviations: CI, confidence interval; ERR, estimated rate ratio; ETD, estimated treatment difference; FPG, fasting plasma glucose; IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine U100; PYE, patient-year of exposure; SD, standard deviation; U, units.

Data are mean (SD) values. Missing data were imputed by unconditional reference-based multiple imputation. Confirmed hypoglycaemia: patient unable to treat themselves and/or have a recorded plasma glucose of <3.1 mmol/L (56 mg/dL).

†26 week retrieved data summary.

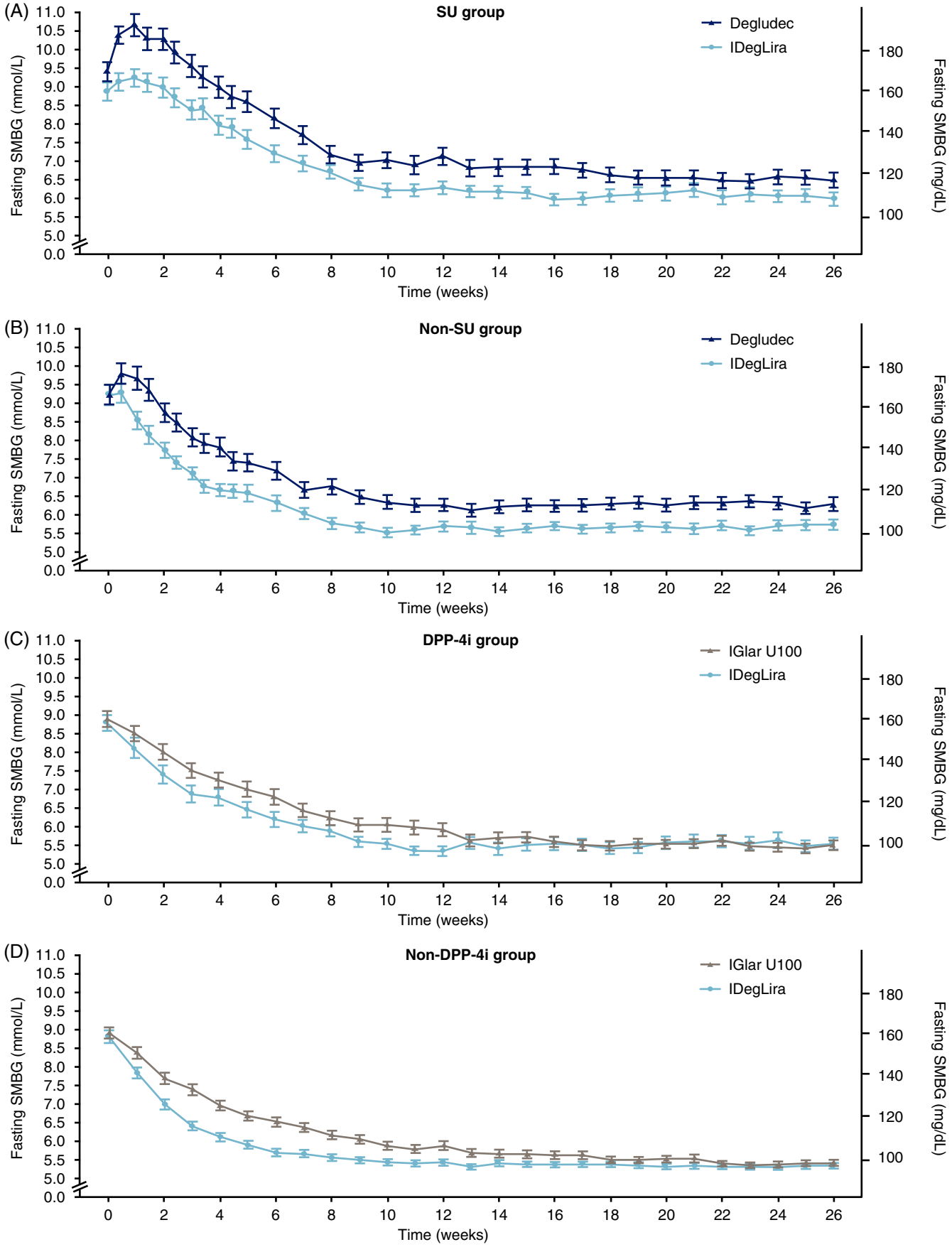

FIGURE 2 Change in mean self-measured blood glucose (SMBG) over 26 weeks by previous (A, B) sulphonylurea (SU) and (C, D) dipeptidyl peptidase-4 inhibitor (DPP4i) use. Data are mean (SEM) and based on the full analysis set. Degludec, insulin degludec; IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine U100; SEM, standard error of the mean

on the glycaemic parameters of the patient as per label. It is often recommended to either reduce SU dose or discontinue SUs altogether, because of the increased risk of hypoglycaemia associated with their combined use.[23] Moreover, the latest guidelines recommend avoiding the use of SUs to reduce the risk of hypoglycaemia, particularly in older patients with T2D.[10] However, as discontinuation of previous OADs can lead to a deterioration in glycaemic control, many patients continue to receive SUs in combination with basal insulin therapy.[24,25] Moreover, there may be a concern among physicians that patients might experience a transient deterioration in glycaemic control when switching to a lower daily insulin dose (16 U) with IDegLira from a previous higher basal insulin dose. Therefore, we aimed to provide data/guidance for clinicians regarding the initiation of IDegLira.

This post hoc analysis of the DUAL II and DUAL IX trials examined the glycaemic control and other efficacy and safety endpoints when initiating IDegLira in subgroups of patients discontinuing pretrial SUs or DPP4is. Overall, regardless of pretrial regimen (SU vs. non-SU or DPP4i vs. non-DPP4i), the outcomes were consistent with the primary results of DUAL II and DUAL IX, which showed that IDegLira improved glycaemic control, with a low rate of hypoglycaemia and no mean weight gain in insulin-naïve patients, and weight loss in patients switching from other basal insulins.[14,20] Furthermore, these analyses show that patients can safely be transitioned to an injectable therapy with discontinuation of pretrial oral medications, with no clinically significant short-term loss of blood glucose control with IDegLira.

The safety and efficacy findings described herein are consistent with the DUAL II primary results, even in those patients who discontinued pretrial SUs. Notably, patients in the SU group did not require a higher dose of IDegLira compared with those in the non-SU group and still achieved similar outcomes. Patients in the SU group were on ~ 30 U of insulin daily at screening, and were switched to 16 U of IDegLira at randomization. There was a small increase in SMBG in the initial 2 weeks, with the greatest increase during the first week, where there was a clinically relevant increase of 1.3 mmol/L (22.5 mg/dL) in the degludec arm. However, improvements were observed from week 4 onwards. Clinicians who are transitioning therapy in patients should be aware of this potential transient rise in SMBG, which on average was clinically irrelevant, and provide reassurance to the patient that with close monitoring and titration any changes will only be during the initial few weeks.

The patients in the SU group of DUAL II had a long diabetes duration, and therefore beta-cell failure may have been extensive.[26,27] It is interesting to note that despite this, favourable outcomes were observed with IDegLira in the SU group, suggesting that although these patients have potentially more impaired beta-cell function, IDegLira still has the ability to improve glycaemic control over basal insulin. This arises from the complementary action of liraglutide, with the effects on beta-cell and alpha-cell function combined with the basal insulin action of degludec.

Similarly, in the DUAL IX trial, there was no evidence of DPP4i discontinuation impacting the treatment effect of IDegLira compared with IGlar U100, as add on to SGLT2i therapy in insulin-naïve patients. Similar reductions in HbA1c, body weight, SMBG and FPG were observed with IDegLira, regardless of antecedent treatment. There was no increase in mean SMBG in the first few weeks after IDegLira initiation at 10 U.

There was no evidence of impact of antecedent treatment on the level of glycaemic control achieved and the safety and efficacy parameters with basal insulin comparators as well as IDegLira. These findings show discontinuation of some OADs is possible without losing glycaemic control, and could help prevent further complications such as hypoglycaemia, particularly within the older adult population. It is important to note that the outcomes observed were achieved with a decrease in regimen complexity in DUAL II, and with minimal increase in regimen complexity in the DUAL IX trial.

The IDegLira regimen used in these trials consisted of a once-daily injection with twice-weekly titration, independent of meals. The efficacy and safety of IDegLira is preserved in real-world use with less stringent dose adjustments as seen with the EXTRA study,[28] and once-weekly dose adjustments as seen in the DUAL VI trial.[18] With combination therapy, basal insulin and GLP-1RA therapy can be initiated together using a simpler regimen than administering separate injections.

The limitations of this study include the post hoc nature of the analysis; the OAD groups compared were not randomized and there were no adjustments made for multiplicity; hence interpretations of these results are limited. As DUAL IX was an open-label trial, this may have introduced bias in the reporting of hypoglycaemic events.

In conclusion, IDegLira was more favourable compared with degludec or glargine U100 in terms of change in HbA1c and body weight, regardless of antecedent treatment. The ETDs for HbA1c were −12.31 mmol/mol (−1.13%) and −4.33 mmol/mol (−0.40%) in the SU and DPP4i groups, respectively. In the non-SU and non-DPP4i groups, the ETDs were −10.32 mmol/mol (−0.94%) and −3.69 mmol/mol (−0.34%), respectively. In the SU and DPP4i groups, the ETDs for body weight were −2.77 and −1.84 kg, respectively. In the non-SU and non-DPP4i groups, the ETDs were −2.41 and −1.95 kg, respectively. Outcomes with IDegLira were achieved with a comparable EOT insulin dose and low hypoglycaemia rates, regardless of pretrial regimen. The results show that the ERRs of hypoglycaemia were 0.56 and 0.41 in the SU and DPP4i groups, respectively, and 0.88 and 0.42 in the non-SU and non-DPP4i groups, respectively. Rates of hypoglycaemia were lower with IDegLira than the comparator in both trials.

Physicians can safely discontinue SUs or DPP4is when initiating IDegLira, without deterioration in glycaemic control and without increase in treatment burden. Clinicians should be aware of a potential transient rise in SMBG when transitioning therapy in patients. With IDegLira, healthcare professionals can offer an intensified treatment to their patients with a single once-daily injection that can be given irrespective of meals, using one pen, and a simple titration method.

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CONFLICT OF INTEREST

A.J. has served as a consultant and is on the speakers' bureau for AstraZeneca, Boehringer Ingelheim, Eli Lilly, MSD, Novo Nordisk and Sanofi. P.O. and K.S.S. are employees and shareholders in Novo Nordisk. K.S. is an employee of Novo Nordisk. A.P.T. receives funding for advisory boards from Scripps Health, and research and education programmes from AZ, Dexcom, Eli Lilly, Novo Nordisk and Sanofi; no direct or indirect reimbursement is provided to the author. L.K.B. receives consulting fees from Sanofi, Dexcom, Eli Lilly and Novo Nordisk, research support from Novo Nordisk and participates in the speakers' bureau for Novo Nordisk.

AUTHOR CONTRIBUTIONS

All of the authors confirm that they meet the International Committee of Medical Journal Editors (ICJME) uniform requirements for authorship and that they have contributed to collection of data, critical analysis and interpretation of the data, drafting/critically revising the article and sharing in the final responsibility for the content of the manuscript and the decision to submit it for publication. A.J. is the guarantor of this work and, as such, had full access to all data in the study and takes responsibility for the integrity of the data.

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SUPPORTING INFORMATION

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

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