

## ORIGINAL ARTICLE

# Rates of hypoglycaemia are lower in patients treated with insulin degludec/liraglutide (IDegLira) than with IDeg or insulin glargine, regardless of the hypoglycaemia definition used

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**Aims:** To re-analyse, using a series of alternative hypoglycaemia definitions, the data from 2 trials, DUAL I and V, in which the once-daily, fixed ratio combination of insulin degludec/liraglutide (IDegLira) was compared with basal insulin therapy.

**Material and Methods:** *Post hoc* analyses of the DUAL I (patients uncontrolled on oral antidiabetic drugs) and DUAL V (patients uncontrolled on insulin glargine (IGlar) U100) trials were carried out using different definitions of hypoglycaemia and according to whether treatments were administered in the morning or afternoon. Rates of hypoglycaemia for the definitions of confirmed and American Diabetes Association (ADA)-documented symptomatic hypoglycaemia were compared according to age, gender and body mass index (BMI).

**Results:** Although hypoglycaemia rates differed according to the alternative hypoglycaemia definitions, rates were consistently lower with IDegLira vs insulin degludec (IDeg) and IGlar U100. Despite glycated haemoglobin concentrations being lower with IDegLira at end of treatment, confirmed and nocturnal-confirmed hypoglycaemia rates were lower for IDegLira vs IDeg and IGlar U100, irrespective of dosing time. The definitions of confirmed and ADA-documented symptomatic hypoglycaemia did not have a significant effect on the treatment difference between IDegLira and IDeg, liraglutide or IGlar U100 when further assessed by baseline age, gender and BMI.

**Conclusions:** Treatment with IDegLira, vs IDeg and IGlar U100, resulted in lower rates of hypoglycaemia regardless of dosing time and definition of hypoglycaemia used. The choice of hypoglycaemia definition did not influence the results of analyses when stratified by age, sex and BMI.

## KEYWORDS

hypoglycaemia, hypoglycaemia rates, IDegLira, insulin degludec, insulin glargine U100, liraglutide

## 1 | INTRODUCTION

Insulin degludec/liraglutide (IDegLira) is a once-daily combination of insulin degludec (IDeg), a basal insulin with a long duration of action,<sup>1</sup> and the glucagon-like peptide-1 receptor agonist (GLP-1RA) liraglutide. In clinical trials, IDegLira has been associated with lower rates of hypoglycaemia vs the basal insulin comparators of IDeg (in the DUAL I clinical trial, NCT01336023)<sup>2</sup> and insulin glargine (IGlar) U100 (in the DUAL V clinical trial, NCT01952145),<sup>3</sup> despite achieving significantly better glycaemic control.

The aim of the present study was to re-analyse, using a series of alternative hypoglycaemia definitions, the data from 2 trials, DUAL I and V, in which IDegLira was compared with basal insulin therapy. In the DUAL I and DUAL V trials, the original definition of confirmed hypoglycaemia used was plasma glucose <3.1 mmol/L (<56 mg/dL) or patient unable to self-treat, and an episode was classified as nocturnal hypoglycaemia if occurring between 12:01 AM and 5:59 AM (both inclusive); however, several other definitions of hypoglycaemia are described in the literature, and have been used across different diabetes clinical trials.<sup>4</sup> The rates of hypoglycaemia reported in a

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clinical trial will inevitably be affected by the definitions used.<sup>5</sup> Recently, the International Hypoglycaemia Study Group released a joint American Diabetes Association (ADA)/European Association for the Study of Diabetes statement stating that a single glucose level should be agreed to, which would allow efficacy of intervention comparisons to be made with greater statistical power.<sup>6</sup> It is also possible that any differences in outcomes associated with differing dosing times, for example, the rate of nocturnal hypoglycaemia, could be masked by the overall hypoglycaemia advantages reported for IDegLira in these studies. The hypoglycaemia results, therefore, were also analysed by dosing time, and by varying the definition of the nocturnal period to better characterize the clinical profile of IDegLira with regard to its relative risks for hypoglycaemia. In addition, previous analyses have shown that IDegLira is efficacious regardless of baseline characteristics, such as BMI<sup>7</sup> and glycated haemoglobin (HbA1c).<sup>8</sup> In the present analysis, we assessed whether the relative risk of hypoglycaemia was influenced by key baseline characteristics, again using the different definitions.

## 2 | MATERIAL AND METHODS

The DUAL I clinical trial compared the efficacy and safety of IDegLira with that of its individual components in insulin-naïve patients with type 2 diabetes previously uncontrolled on metformin with or without pioglitazone. Patients were randomized 2:1:1 to receive IDegLira (n = 834), IDeg (n = 414) or liraglutide (n = 415) over the 26-week main trial period<sup>2</sup>; a total of 1311 patients continued treatment into the 26-week extension period (ext); 665, 333 and 313 patients for IDegLira, IDeg and liraglutide, respectively.<sup>7</sup> IDegLira treatment was initiated at 10 dose steps daily (10 units of IDeg plus 0.36 mg of liraglutide); similarly, IDeg treatment was initiated at 10 units daily. Liraglutide treatment was initiated at a daily dose of 0.6 mg, increased by 0.6 mg each week, until a final dose of 1.8 mg/d was reached. IDegLira and IDeg were titrated twice weekly to a fasting plasma glucose

target of 4 to 5 mmol/L (72-90 mg/dL), with a maximum dose of 50 dose steps for IDegLira, but no maximum dose for IDeg.<sup>7</sup>

In the DUAL V trial, IDegLira was compared with continued up-titration of IGlir U100 in patients with type 2 diabetes previously uncontrolled on IGlir U100 (20-50 units daily) and metformin.<sup>3</sup> A total of 557 patients were randomized 1:1 to receive IDegLira or IGlir U100 (278 and 279 patients, respectively) over a 26-week period. IDegLira was initiated at 16 dose steps (16 units of IDeg plus 0.58 mg of liraglutide) administered once daily at any time of day, although preferably at the same time of day throughout the trial. Meanwhile, IGlir U100 was continued at pre-trial daily dose and administered once daily according to local prescribing instructions. Similarly to DUAL I, IDegLira and IGlir U100 were titrated twice weekly to a fasting plasma glucose target of 4 to 5 mmol/L with a maximum dose of 50 dose steps for IDegLira, but no maximum dose for IGlir U100.<sup>3</sup>

*Post hoc* analyses of the DUAL I/ext and DUAL V trial data were carried out according to different definitions of hypoglycaemia (Table 1) and according to whether both treatments were administered in the morning (12:00-11:59 AM) or the afternoon (12:00-11:59 PM). In addition, the rates of hypoglycaemia for the definitions of confirmed hypoglycaemia and ADA-documented symptomatic hypoglycaemia were compared with patient data stratified according to the baseline characteristics of age (<65 and ≥65 years), gender and body mass index (BMI; <25, ≥25 to <30, ≥30 to <35 and ≥35 kg/m<sup>2</sup>). The proportions of patients achieving an HbA1c concentration of either <7% or ≤6.5%, the proportions achieving these targets with no confirmed hypoglycaemia, and those achieving these targets with no confirmed hypoglycaemia and no weight gain, has been described previously for DUAL I<sup>2</sup> and DUAL V<sup>3</sup>; hypoglycaemia was defined in these reports as the patient being unable to self-treat or plasma glucose <3.1 mmol/L (<56 mg/dL). In the present *post hoc* analysis we examined the same endpoints using the ADA-documented symptomatic hypoglycaemia definition (Table 1). Protocols were approved by institutional review boards and studies were carried out in accordance with the Declaration of Helsinki.

**TABLE 1** Description of different hypoglycaemia definitions used in analyses

Analysis	Description
<b>Definition of hypoglycaemia</b>	
Confirmed hypoglycaemia (original)	Episodes confirmed by a plasma glucose <3.1 mmol/L (<56 mg/dL) and/or unable to self-treat
Overall confirmed symptomatic hypoglycaemia	Episodes confirmed by a plasma glucose <3.1 mmol/L (<56 mg/dL) and/or unable to self-treat, accompanied by reported symptoms
ADA-documented symptomatic hypoglycaemia	Symptomatic episodes confirmed by a plasma glucose ≤3.9 mmol/L (≤70 mg/dL)
<b>Timescales for nocturnal period</b>	
Nocturnal confirmed hypoglycaemia (12:01-5:59 AM)	Episodes confirmed by a plasma glucose <3.1 mmol/L (<56 mg/dL) and/or unable to self-treat occurring between 12:01 and 5:59 AM (both inclusive)
Nocturnal confirmed symptomatic hypoglycaemia	Symptomatic episodes confirmed by a plasma glucose <3.1 mmol/L (<56 mg/dL) and/or unable to self-treat, occurring between 12:01 and 5:59 AM (both inclusive)
Nocturnal ADA-documented symptomatic hypoglycaemia	Symptomatic episodes confirmed by a plasma glucose ≤3.9 mmol/L (≤70 mg/dL) occurring between 12:01 and 5:59 AM (both inclusive)
Nocturnal confirmed hypoglycaemia (9:59 PM to 5:59 AM)	Episodes confirmed by a plasma glucose <3.1 mmol/L (<56 mg/dL) and/or unable to self-treat occurring between 9:59 PM and 05:59 AM (both inclusive)
Nocturnal confirmed hypoglycaemia (12:01-7:59 AM)	Episodes confirmed by a plasma glucose <3.1 mmol/L (<56 mg/dL) and/or unable to self-treat occurring between 12:01 and 7:59 AM (both inclusive)

## 2.1 | Statistical methods

The number of hypoglycaemic events according to the definition of hypoglycaemia, dosing time and baseline characteristics was analysed based on the full analysis set using a negative binomial regression model with a log link and the logarithm of the time period in which a hypoglycaemic episode was considered treatment-emergent as offset. The model included treatment, country/region and relevant stratification factors (in DUAL I/ext only) of previous OAD treatment, baseline HbA1c stratum and substudy participation as fixed effects. Analyses of hypoglycaemia according to baseline characteristics further included the baseline group and an interaction term between baseline group and treatment as fixed effects in the model. For the proportion of patients achieving HbA1c targets, odds ratios were estimated from a logistic regression model, with treatment, region and relevant stratification factors as fixed factors, and baseline HbA1c and weight, when weight was included in the composite, as covariates.

## 3 | RESULTS

### 3.1 | Hypoglycaemia rates according to different definitions

Regardless of the hypoglycaemia definition used, rates of hypoglycaemia were lower in patients treated with IDegLira than with IDeg, for both DUAL I and DUAL I ext, or with IGLar U100 in DUAL V, but higher than in patients treated with liraglutide, for both DUAL I and DUAL I ext (Table 2). The lower hypoglycaemia rates in comparison with basal insulin therapy with IDeg or IGLar U100 were achieved, despite significantly greater end-of-trial HbA1c reductions with IDegLira therapy.<sup>2,3,7</sup>

Estimated rate ratios for hypoglycaemia by treatment were statistically significantly lower for patients treated with IDegLira compared with IDeg or IGLar U100 for all definitions of overall hypoglycaemia, including confirmed symptomatic and ADA-documented symptomatic episodes (DUAL I ext and DUAL V shown in Figure 1, DUAL I shown in Figure S1). Very few of the total hypoglycaemia events were categorized as severe (an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions); in DUAL I there were 3 severe events with IDegLira, 2 with IDeg and none with liraglutide, in DUAL I ext, at the end of 52 weeks there were 3 severe events with IDegLira (those reported in the main DUAL I trial), 2 with IDeg (those reported in the main DUAL I trial) and 2 with liraglutide,<sup>7</sup> and in DUAL V one severe event with IGLar U100 and none with IDegLira.<sup>3</sup> For nocturnal hypoglycaemia, rates were statistically significantly lower in patients treated with IDegLira than with IDeg for both DUAL I and DUAL I ext for the definition of nocturnal confirmed hypoglycaemia (unable to self-treat or  $<3.1$  mmol/L [ $<56$  mg/dL], 12:01-7:59 AM). For the nocturnal ADA-documented symptomatic hypoglycaemia definition, the rate was significantly lower with IDegLira in DUAL I ext (Figure 1A). Liraglutide treatment, in comparison with IDegLira, resulted in statistically significantly lower rates of hypoglycaemia in DUAL I and DUAL I ext for all definitions except nocturnal confirmed

symptomatic hypoglycaemia, where statistical analyses could not be carried out because of the low number of events in the liraglutide arm.

The cumulative mean numbers of ADA-documented symptomatic episodes per patient for IDegLira, IDeg and liraglutide from DUAL I and DUAL I ext are shown in Figure 2A, and for IDegLira and IGLar U100 from DUAL V, in Figure 2B. The equivalent data for nocturnal ADA-documented symptomatic hypoglycaemia are given in Figure S2. For comparison, the cumulative mean number of overall and nocturnal events per patient, by treatment, using the original confirmed hypoglycaemia definition can be seen in Figure S3.

### 3.2 | Hypoglycaemia rates by dosing time

Confirmed hypoglycaemia rates for IDegLira, IDeg and liraglutide when all treatments were dosed in the morning were 1.68, 2.76 and 0.22 events per patient-years of exposure (PYE), respectively, in DUAL I, and the rates were 1.66, 3.11 and 0.18 events per PYE in DUAL I ext. When all treatments were dosed in the afternoon, confirmed hypoglycaemia rates for IDegLira, IDeg and liraglutide were 1.94, 2.42 and 0.22 events per PYE, respectively, in DUAL I, and 1.89, 2.53 and 0.20 events per PYE, respectively, in DUAL I ext. Nocturnal confirmed hypoglycaemia rates for IDegLira, IDeg and liraglutide when all treatments were dosed in the morning were 0.22, 0.29 and 0.01 events per PYE, respectively, in DUAL I, and 0.22, 0.48 and 0.01 events per PYE, respectively, in DUAL I ext. When all treatments were dosed in the afternoon, the respective confirmed nocturnal hypoglycaemia rates were 0.23, 0.27 and 0.05 events per PYE in DUAL I, and 0.23, 0.27 and 0.03 events per PYE in DUAL I ext. The estimated rate ratios for DUAL I and DUAL I ext show that, in patients treated with IDegLira, confirmed hypoglycaemia rates were statistically significantly lower than with IDeg for morning-dosing of both treatments; for afternoon-dosing of both treatments, a statistically significant difference between IDegLira and IDeg treatment was observed in DUAL I ext (Figure 3A). Nocturnal confirmed hypoglycaemia rates were lower in patients treated with IDegLira than with IDeg, but the difference was only statistically significant for morning-dosing of both treatments in DUAL I ext. For afternoon-dosing, there was no statistically significant difference between treatment with IDegLira and treatment with IDeg in DUAL I or DUAL I ext for nocturnal hypoglycaemia (Figure 3A). Compared with IDegLira, treatment with liraglutide resulted in statistically significantly lower rates of confirmed and nocturnal confirmed hypoglycaemia, whether both treatments were dosed in the morning or afternoon, for both DUAL I and DUAL I ext (Figure 2B). Confirmed hypoglycaemia rates for IDegLira and IGLar U100 were 2.18 and 6.86 events per PYE, respectively, when dosed in the morning and 2.26 and 4.59 events per PYE when dosed in the afternoon. Nocturnal confirmed hypoglycaemia rates were 0.22 and 1.67 events per PYE, for IDegLira and IGLar U100, respectively, when both treatments were dosed in the morning and 0.23 and 1.12 events per PYE when dosed in the afternoon. IDegLira treatment resulted in statistically significantly lower rates of confirmed and nocturnal confirmed hypoglycaemia than IGLar U100, whether both treatments were dosed in the morning or afternoon (Figure 3C).

**TABLE 2** Observed rates of hypoglycaemia

DUAL I: IDegLira (n = 825), IDeg (n = 412), liraglutide (n = 412)	Episodes per PYE		
	IDegLira	IDeg	Liraglutide
Confirmed hypoglycaemia (original)			
Main trial period	1.80	2.56	0.22
Trial extension period	1.77	2.79	0.19
Overall confirmed symptomatic hypoglycaemia			
Main trial period	0.67	1.08	0.06
Trial extension period	0.70	1.13	0.07
ADA-documented symptomatic hypoglycaemia			
Main trial period	4.12	5.74	0.35
Trial extension period	4.20	6.40	0.37
Nocturnal confirmed hypoglycaemia (12:01-5:59 AM)			
Main trial period	0.22	0.28	0.03
Trial extension period	0.22	0.37	0.02
Nocturnal confirmed symptomatic hypoglycaemia			
Main trial period	0.08	0.10	NA
Trial extension period	0.09	0.14	NA
Nocturnal ADA-documented symptomatic hypoglycaemia			
Main trial period	0.54	0.66	0.05
Trial extension period	0.52	0.83	0.03
Nocturnal confirmed hypoglycaemia (9:59 PM to 5:59 AM)			
Main trial period	0.24	0.26	0.02
Trial extension period	0.25	0.32	0.03
Nocturnal confirmed hypoglycaemia (12:01-7:59 AM)			
Main trial period	0.76	1.15	0.09
Trial extension period	0.78	1.31	0.07
DUAL V: IDegLira (n = 278), insulin glargine U100 (n = 279)	IDegLira	IGlar U100	
Confirmed hypoglycaemia (original)	2.23	5.05	
Overall confirmed symptomatic hypoglycaemia	1.56	3.75	
ADA-documented symptomatic hypoglycaemia	8.03	15.63	
Nocturnal confirmed hypoglycaemia (00:01-05:59 h)	0.22	1.23	
Nocturnal confirmed symptomatic hypoglycaemia	0.16	1.02	
Nocturnal ADA-documented symptomatic hypoglycaemia	0.72	2.75	
Nocturnal confirmed hypoglycaemia (9:59 to 5:59 AM)	0.27	1.35	
Nocturnal confirmed hypoglycaemia (12:01-7:59 AM)	1.17	2.94	

Abbreviation: NA, not applicable.

Data based on the safety analysis set.

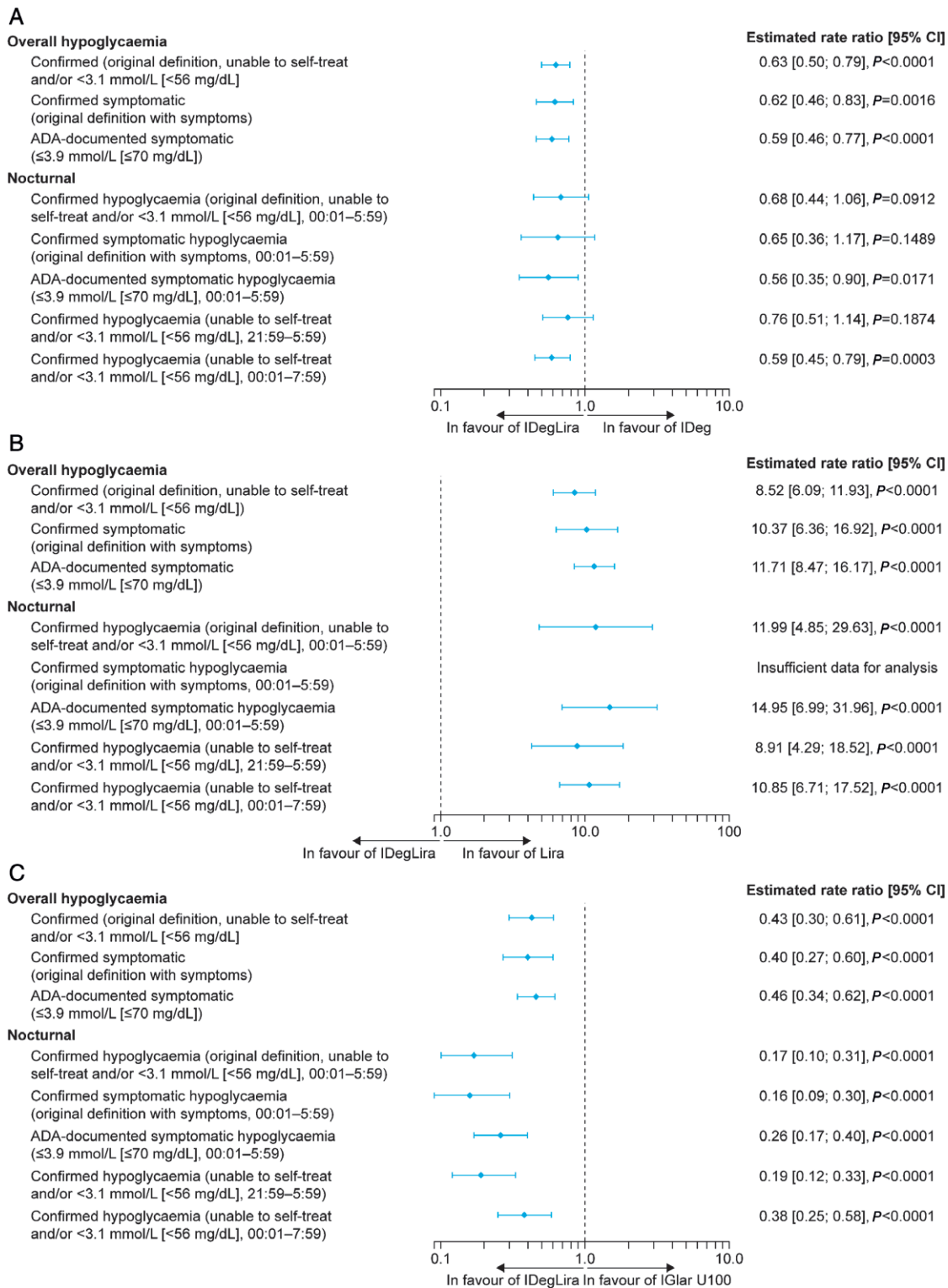
### 3.3 | Confirmed and ADA-documented symptomatic hypoglycaemia rates by baseline characteristics

The analyses of confirmed hypoglycaemia and ADA-documented symptomatic hypoglycaemia definitions, according to baseline characteristics of age, gender and BMI, showed generally consistent rates for both hypoglycaemia definitions for DUAL I (Table S1A) and DUAL V (Table S1B) between the treatment groups. Interaction analyses showed there was no statistically significant effect of age, gender or BMI on the estimated treatment rate ratio for IDegLira vs IDeg for both confirmed and ADA-documented symptomatic hypoglycaemia (all  $P > .10$ ). Comparing IDegLira with liraglutide, there was no statistically significant effect of age, gender or BMI on the estimated treatment rate ratio for confirmed hypoglycaemia ( $P = .2565$ ,  $P = .2635$  and  $P = .2372$ , respectively), but while gender and BMI had no

significant effect on ADA-documented symptomatic hypoglycaemia rate ratio ( $P = .2090$  and  $P = .0659$ , respectively), there was a significant difference seen between age  $<65$  and  $\geq 65$  years ( $P = .025$ ), with the rate ratio (favouring liraglutide) being much greater for patients aged  $>65$  years using this definition.

### 3.4 | Proportion of patients achieving combined endpoints

The proportions of patients achieving an HbA1c concentration of  $<7\%$ , or of  $\leq 6.5\%$ , those achieving the HbA1c targets with no ADA-documented symptomatic hypoglycaemia, and those achieving these targets with no ADA-documented symptomatic hypoglycaemia and no weight gain are given in Table S2. The odds of achieving an HbA1c concentration  $<7\%$  or  $\leq 6.5\%$  without ADA-documented symptomatic

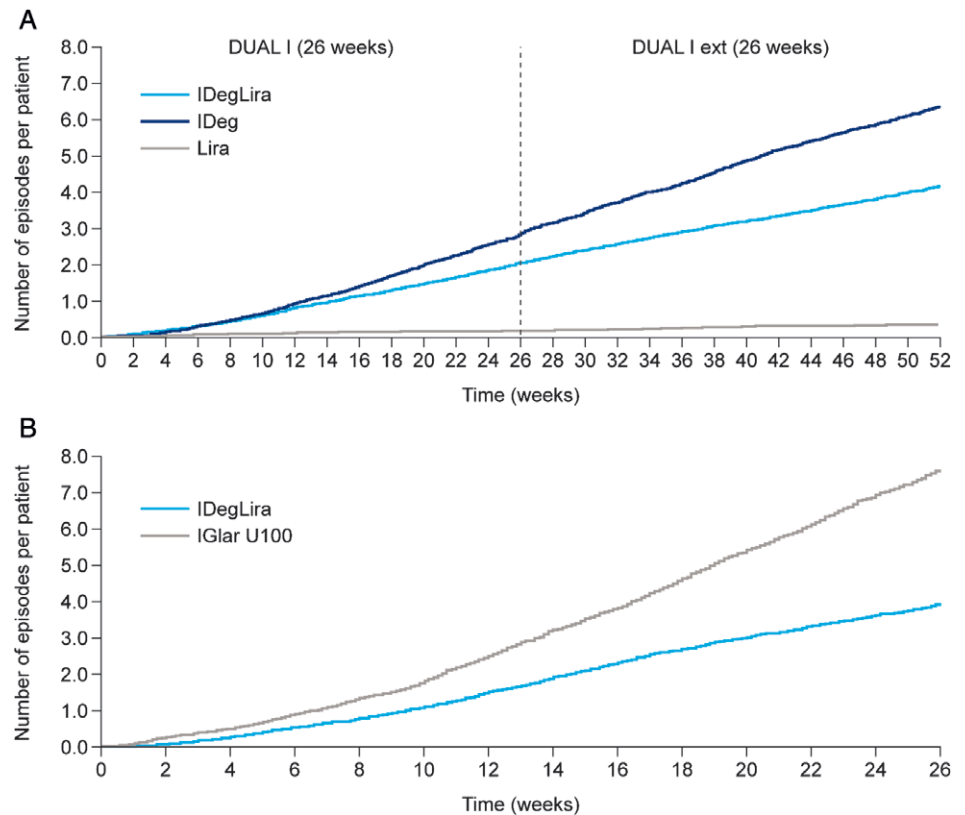


**FIGURE 1** Estimated rate ratio of hypoglycaemia by hypoglycaemia definition for A, IDegLira vs IDeg and B, IDegLira vs liraglutide for DUAL I ext and C, IDegLira vs IGlir U100 for DUAL V. Data based on the full analysis set. The number of hypoglycaemic events was analysed using a negative binomial regression model with a log link and the logarithm of the time period in which a hypoglycaemic episode was considered treatment-emergent as offset. The model included treatment, country/region and relevant stratification factors (in DUAL I ext only) of previous OAD treatment, baseline HbA1c stratum, and substudy participation as fixed effects. CI, confidence interval; OAD, oral antidiabetic drug

hypoglycaemia and without ADA-documented symptomatic hypoglycaemia and weight gain were significantly greater with IDegLira than with IDeg and IGlir U100 ( $P < .0001$  for all comparisons). A greater proportion of patients reached these targets with liraglutide than with

IDegLira, and this difference in odds was significant for HbA1c  $< 7\%$  with no ADA-documented symptomatic hypoglycaemia or weight gain ( $P < .0001$ ), HbA1c of  $\leq 6.5\%$  with no ADA-documented symptomatic hypoglycaemia ( $P = .0006$ ) and HbA1c  $\leq 6.5\%$  with no ADA-





**FIGURE 2** Cumulative mean number of ADA-documented symptomatic hypoglycaemic episodes per patient for A, IDegLira, IDeg and liraglutide for DUAL I and DUAL I ext and (B) IDegLira and IGlax U100 in DUAL V. Data based on the safety analysis set. ADA-documented symptomatic hypoglycaemic episode defined as typical symptoms of hypoglycaemia confirmed by a plasma glucose  $\leq 3.9$  mmol/L ( $\leq 70$  mg/dL)

documented symptomatic hypoglycaemia or weight gain ( $P = .0061$ ). It was not significantly different for HbA1c  $< 7\%$  with no ADA-documented symptomatic hypoglycaemia ( $P = .9075$ ).

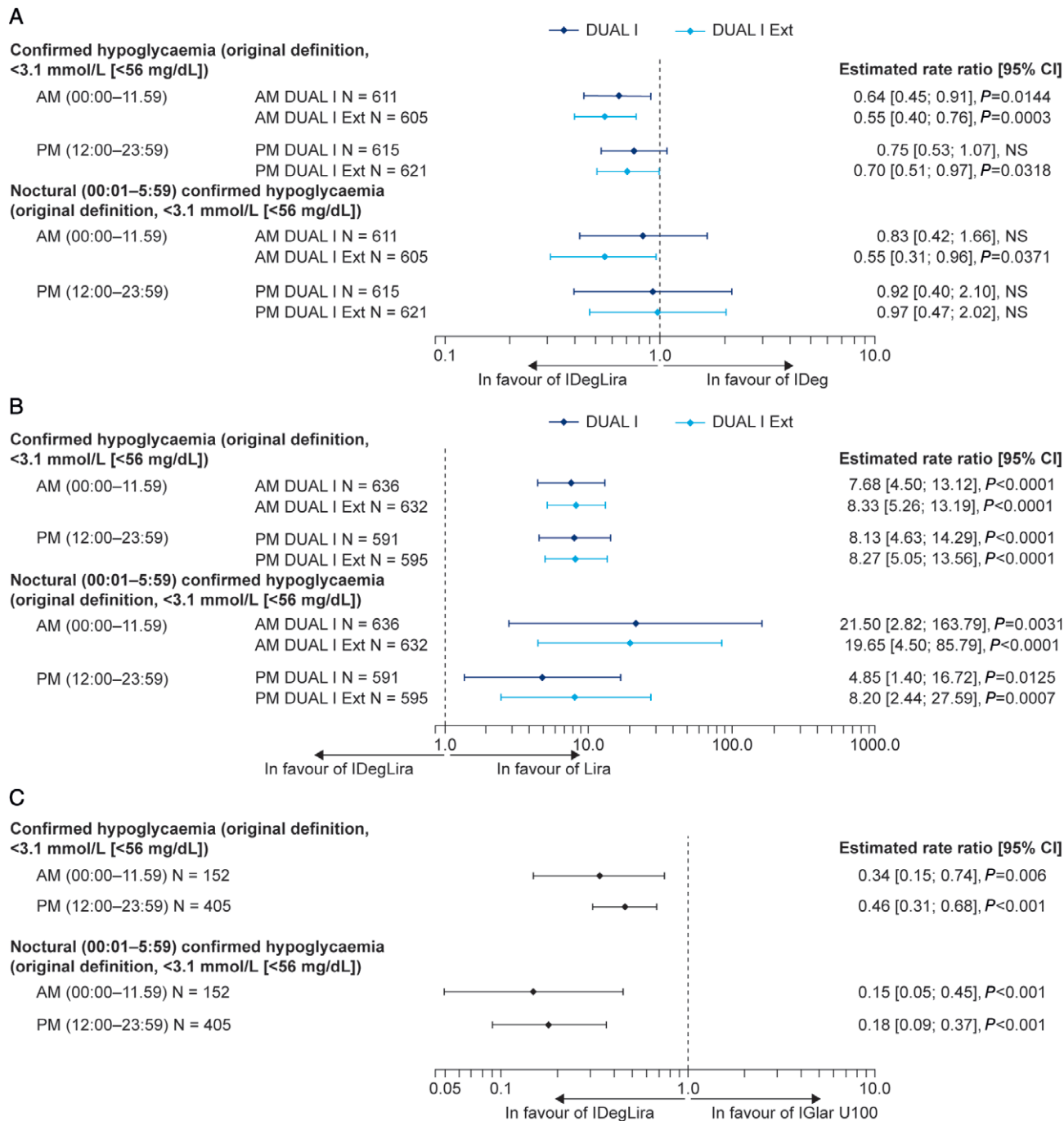
## 4 | DISCUSSION

IDegLira treatment has previously been shown to result in greater improvements in glycaemic control than IDeg<sup>2,7</sup> or IGlax U100<sup>3</sup> and, despite the greater HbA1c reduction, hypoglycaemia rates were lower. The present *post hoc* analyses extend this finding to show that confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia rates were lower for IDegLira in comparison with IDeg and IGlax U100, irrespective of dosing time, and regardless of the hypoglycaemia definitions used. One explanation for the lower rates of hypoglycaemia is the glucose-dependent mode of action of GLP-1RAs concomitant to the insulin-sparing effect when GLP-1RAs are used together with insulin.<sup>2</sup> One of the findings of the present analysis was that the advantage of IDegLira with regard to nocturnal hypoglycaemia was unaffected by the definition of the nocturnal period. It is possible that the insulin degludec component of IDegLira becomes a more critical determinant of risk in the nocturnal period because IDeg is associated with low variability in the glucose-lowering effect across 24 hours and from day to day.<sup>9</sup> Importantly, a similar finding was made in a meta-analysis of data from trials comparing IDeg with IGlax U100.<sup>10</sup> In that meta-analysis, the number of episodes per PYE was again similar across different definitions of nocturnal hypoglycaemia, and the advantage of IDeg was preserved.<sup>10</sup>

The definition of ADA-documented symptomatic hypoglycaemia resulted in greater numbers of episodes per PYE than the original

definition and this is primarily attributable to the raised glycaemic threshold at which hypoglycaemia is recognized in the ADA definition ( $\leq 3.9$  mmol/L [ $\leq 70$  mg/dL] as opposed to  $< 3.1$  mmol/L [ $< 56$  mg/dL]), combined with the low titration target applied in the trials (4.0–5.0 mmol/L). Higher event rates were also produced by changing the definition of the nocturnal period to 12:01 to 07:59 AM, possibly as a result of this including the pre-breakfast self-monitored plasma glucose measurement and/or the influence of diabetes therapies within this interval when taken at an early breakfast. The profiles for IDegLira, IDeg and liraglutide with regard to the overall and nocturnal cumulative mean number of episodes per patient for DUAL I and DUAL I ext using the ADA-documented symptomatic hypoglycaemia definition were, however, similar to those previously published with the original definitions,<sup>7</sup> albeit that the number of episodes per PYE was higher with the ADA definition. A similar pattern was seen for the profiles of cumulative mean number of episodes per patient for IDegLira and IGlax U100 for ADA-documented symptomatic episodes in comparison to those previously published for confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia.<sup>3</sup> The profiles of the cumulative mean number of episodes continued to diverge throughout the trial, indicating that the difference was not just an effect of the titration phase; rather, the benefit appeared to be maintained or even to increase with time over the course of the trial.

The comparisons of confirmed hypoglycaemia and ADA-documented symptomatic hypoglycaemia according to the baseline characteristics indicated consistency in the treatment difference between IDegLira and IDeg, liraglutide or IGlax U100, for either hypoglycaemia definition, across the age, sex and BMI categories. Overall, the outcomes according to age, sex and BMI further highlight the



**FIGURE 3** Estimated rate ratio of hypoglycaemia (based on original definition) by dosing time for A, IDegLira vs IDeg and B, IDegLira vs liraglutide for DUAL I and DUAL I ext and C, IDegLira vs IGlir U100 for DUAL V. Data based on the full analysis set. The number of hypoglycaemic events was analysed using a negative binomial regression model with a log link and the logarithm of the time period in which a hypoglycaemic episode was considered treatment-emergent as offset. The model included treatment, country/region and relevant stratification factors (in DUAL I/ext only) of previous OAD treatment, baseline HbA1c stratum, and substudy participation as fixed effects. CI, confidence interval; OAD, oral antidiabetic drug

benefits of treatment with IDegLira across a variety of populations of patients with type 2 diabetes.<sup>7,11</sup>

A limitation of the present study is that patients were not randomized according to dosing time. A further consideration is that hypoglycaemia data from randomized controlled trials are not necessarily indicative of real-world hypoglycaemia rates, which tend to be higher.<sup>12</sup> This may mean that the benefits of lower hypoglycaemia rates with IDegLira treatment, vs IDeg and IGlir U100,

could be even greater in a clinical setting; however, this remains to be demonstrated, because in practice patients may not be titrated to such tight targets as in the trial setting. Another limitation of the present study is that the analyses were not adjusted for multiplicity.

In conclusion, treatment with IDegLira, in comparison with IDeg and IGlir U100, results in lower rates of hypoglycaemia, regardless of dosing time and definition of hypoglycaemia used. This effect is

observed despite lower HbA<sub>1c</sub> levels being achieved with IDegLira compared with IDeg and IGLar U100. Furthermore, the baseline characteristics of sex and BMI did not have a significant effect on the rate ratios across different hypoglycaemia definitions. Patients aged >65 years had a greater reduction in hypoglycaemia than patients aged <65 years; therefore, a broad variety of patients with type 2 diabetes might expect to reach their treatment targets with low hypoglycaemia rates during treatment with IDegLira.

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## Conflict of interest

P. N. has received research funding from Novo Nordisk and works with Eli Lilly, Sanofi, AstraZeneca and other companies. R. C. has appeared on speakers' bureau or advisory boards for Novo Nordisk, Merck Sharp & Dohme, AstraZeneca, Eli Lilly & Co, Boehringer Ingelheim, Amgen and Sanofi Aventis. E. J. has received research support from Novo Nordisk, Novartis, Gilead, Roche, Miltenyi Biotech, Biotest, Wacker Chemie, Fresenius DFG, BMBF, EU, JDRF, VW-Stiftung and has appeared on speakers' bureau or advisory boards for Novo Nordisk, Eli Lilly, AstraZeneca, Boehringer Ingelheim, MSD, Janssen, Roche and Novartis. UT Southwestern (on behalf of I. L.) received research funding and/or consulting fees from NovoNordisk, Novartis, GIDynamics, Merck and Pfizer. I.L. received non-financial support from Novo Nordisk, Sanofi, AstraZeneca and Boehringer Ingelheim. S. H. has served on scientific advisory boards and provided consultancy for which his institution has received remuneration from Eli Lilly & Co, Novo Nordisk, Takeda, Merck Sharp & Dohme and Becton Dickinson. S. H. has also served as a speaker for which he received remuneration from AstraZeneca, Eli Lilly & Co, Novo Nordisk, Boehringer Ingelheim and Takeda and has received research support from Medtronic UK Ltd. H. J. is an employee and shareholder of Novo Nordisk. L. L. is an employee and shareholder of Novo Nordisk.

## Author contributions

P. N., E. J., I. L., L. L. and H. J. made substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data; E. J., I. L., L. L. and H. J. participated in drafting the article or revising it critically for important intellectual content; and P. N., R. C., E. J., I. L., H. J., L. L. and S. H. gave final approval of the version to be submitted and any revised version.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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