

## ORIGINAL ARTICLE

# Safety and efficacy of IDegLira titrated once weekly versus twice weekly in patients with type 2 diabetes uncontrolled on oral antidiabetic drugs: DUAL VI randomized clinical trial

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**Aims:** To compare the safety and efficacy of a simpler titration algorithm for insulin degludec/liraglutide (IDegLira) with that used in previous DUAL trials in insulin-naïve patients with type 2 diabetes.

**Research design and methods:** This 32-week, open-label, non-inferiority trial randomized adults with type 2 diabetes uncontrolled on metformin ± pioglitazone to receive IDegLira, titrated either once weekly, based on the mean of 2 pre-breakfast plasma glucose (PG) readings (n = 210), or twice weekly, based on the mean of 3 pre-breakfast PG readings (n = 210).

**Results:** Mean HbA1c decreased from 8.2% (65 mmol/mol) to 6.1% (43 mmol/mol) with once-weekly titration and from 8.1% (65 mmol/mol) to 6.0% (42 mmol/mol) with twice-weekly titration; non-inferiority was confirmed (estimated treatment difference: 0.12% [-0.04; 0.28]<sub>95% CI</sub>, 1.30 mmol/mol [-0.41; 3.01]<sub>95% CI</sub>). Approximately 90% of patients achieved HbA1c < 7% in each arm. Mean fasting PG was similar after 32 weeks. Weight change was -1.0 kg vs -2.0 kg for once-weekly vs twice-weekly titration. Rates of severe or blood glucose-confirmed symptomatic hypoglycaemia were low in both arms: 0.16 events/patient-year of exposure (PYE) for once-weekly, 0.76 events/PYE for twice-weekly titration. Mean IDegLira dose at 32 weeks was 41 dose steps (41 U IDeg/1.48 mg Lira) for both arms. Overall adverse event rates were 207.8 and 241.3 events/100 PYE with once-weekly and twice-weekly titration, respectively.

**Conclusion:** A pragmatic titration algorithm with once-weekly adjustments based on 2 PG readings resulted in a safety and glycaemic efficacy profile similar to that with twice-weekly adjustments based on 3 preceding PG values in insulin-naïve patients.

## KEYWORDS

efficacy, insulin therapy, randomized clinical trials, safety, type 2 diabetes

## 1 | INTRODUCTION

The progressive nature of type 2 diabetes means that the majority of patients may eventually require insulin therapy,<sup>1,2</sup> but insulin initiation is often delayed for several years until glycaemic control has deteriorated well beyond guideline targets.<sup>3</sup> Reasons for this clinical inertia include patient fear of unwanted side

effects such as hypoglycaemia and weight gain, fear of injections, the belief that quality of life will worsen considerably and the belief that adherence to increasingly complex regimens will prove too challenging.<sup>4,5</sup> However, evidence of an inverse correlation between regimen complexity and patient adherence<sup>6,7</sup> suggests that simpler treatment regimens could do much to tackle clinical inertia.

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In recent years, the effectiveness of combining basal insulin therapy with glucagon-like peptide-1 receptor agonist (GLP-1RA) therapy has been demonstrated, and is reflected in the joint statement from the American Diabetes Association and the European Association for the Study of Diabetes.<sup>8</sup> GLP-1RAs stimulate insulin secretion while suppressing glucagon release in a glucose-dependent manner,<sup>9</sup> and are associated with weight loss and a low risk of hypoglycaemia; however, transient gastrointestinal (GI) side effects are common with initial GLP-1RA therapy.<sup>10,11</sup> Once-daily GLP-1RAs can be combined with once-daily basal insulins as fixed-ratio combination products such as insulin degludec with liraglutide (IDegLira) and insulin glargine with lixisenatide (iGlarLixi),<sup>12-18</sup> thereby simplifying treatment escalation. The clinical utility of IDegLira has been demonstrated previously in patients with type 2 diabetes uncontrolled by oral antidiabetic drugs (OADs), GLP-1RA therapy and basal insulin therapy in the phase 3 DUAL trials I to V.<sup>13-17</sup> Results from DUAL I, a phase 3a trial,<sup>13,14</sup> demonstrate that IDegLira combines the clinical advantages and limits the principal side effects of basal insulin (weight gain, hypoglycaemia) and GLP-1RA (GI side effects) therapy, and is insulin-sparing as compared to basal insulin alone.

Alternative titration algorithms can simplify regimen complexity, and thereby help empower patients to manage their diabetes more conveniently and effectively, as demonstrated in AT.LANTUS<sup>19</sup> and the INSIGHT study.<sup>20</sup> The present trial assessed whether similar glycaemic control and tolerability could be achieved with IDegLira using a simpler, more pragmatic once-weekly titration algorithm in insulin-naïve patients with type 2 diabetes uncontrolled with OADs than previously employed in the DUAL clinical programme. Therefore, this trial investigated the safety and efficacy of IDegLira titrated once weekly, based on the mean of 2 pre-breakfast plasma glucose (PG) measurements, vs twice-weekly titration, based on the mean of 3 pre-breakfast PG readings (ie, 6 measurements and 2 dose adjustments per week).

## 2 | RESEARCH DESIGN AND METHODS

### 2.1 | Study design and participants

This phase 3b, 32-week, randomized, open-label, parallel-group trial was conducted at 80 sites in 9 countries (Table S1, Appendix S1) between November 2014 and December 2015. The trial protocol, consent form and information sheet were approved by appropriate health authorities and independent ethics committee/institutional review boards. Written informed consent was obtained from participants before enrolment. The trial was performed in accordance with the Declaration of Helsinki<sup>21</sup> and ICH Good Clinical Practice (GCP).<sup>22</sup>

Adults (aged  $\geq 18$  years) with type 2 diabetes, glycated haemoglobin (HbA1c) of 7.0% to 10.0% (53-86 mmol/mol; both inclusive), BMI  $\leq 40$  kg/m<sup>2</sup> and who had been treated previously with a stable daily dose of metformin ( $\geq 1500$  mg or maximum tolerated dose) with or without pioglitazone ( $\geq 30$  mg) for at least 90 days before screening were eligible for enrolment. Patients were insulin-naïve and could

not have been treated with any drugs other than metformin and pioglitazone that could interfere with blood glucose (BG) levels within 90 days before the screening visit (Table S2, Appendix S1 lists all inclusion and exclusion criteria).

### 2.2 | Randomization and masking

Participants were randomized using a central interactive voice/web system in a 1:1 ratio to receive once-daily, subcutaneous injections of IDegLira (100 units/mL IDeg: 3.6 mg/mL liraglutide; 3 mL prefilled PDS290 pen-injector; Novo Nordisk, Bagsværd, Denmark) titrated either once weekly (n = 210) or twice weekly (n = 210) (Figure S1, Appendix S1). An external independent event adjudication committee (EAC) performed ongoing adjudication and standardized assessment of selected events. An independent committee of thyroid experts regularly monitored plasma calcitonin levels.

The trial was open-label as all patients in both treatment arms received IDegLira and it was the 2 different titration algorithms that were compared. Furthermore, the frequency of self-measured plasma glucose (SMPG) measurements was different in the 2 arms, making blinding unfeasible.

### 2.3 | Procedures

Metformin was maintained at pre-trial dose and frequency, unless there was a safety concern. At randomization, IDegLira was initiated at 10 dose steps. One dose step of IDegLira contains 1 unit of IDeg + 0.036 mg of liraglutide. In the once-weekly titration group, the dose of IDegLira was adjusted once weekly based on the mean of 2 fasting SMPG values measured pre-breakfast in the morning of 2 consecutive days, corresponding to 1 obtained on the day before titration and 1 obtained on the day of titration. It was recommended that titration be performed on the same day of the week throughout the trial for individual patients. In the twice-weekly titration group, the dose of IDegLira was to be adjusted twice weekly, every 3 to 4 days. Titration was to be based on the mean of 3 fasting SMPG values obtained pre-breakfast in the morning of 3 consecutive days, corresponding to one obtained on each of the 2 days before titration and one obtained on the day of titration. In both treatment groups, adjustments were to be made in increments or decrements of 2 dose steps with titration to a fasting glycaemic target of 72 to 90 mg/dL (4.0-5.0 mmol/L) (Figure S1, Appendix S1). Participants performed BG monitoring with a glucose meter (Abbott Diabetes Care, Abbott Park, Illinois; model dependent on local availability), calibrated to plasma values; meters were used according to the manufacturer's instructions. Novo Nordisk ensured continuous safety surveillance and monitoring of titration; the trial staff emphasized the importance of adherence to trial protocol at every visit and the residual IDegLira pen volume was assessed at visits 6, 10, 14, 18, 22, 28 and 34, with any discrepancies put forward to the participant for discussion. In addition, the investigator was to assess the compliance of the participant at each visit based on a review of glycaemic control, adherence to the visit schedule and completion of the participant's diary, including SMPG profiles.

## 2.4 | Outcome measures

The primary endpoint was change from baseline in HbA1c after 32 weeks of treatment. Supportive secondary efficacy endpoints included the percentages of patients achieving end-of-trial HbA1c targets  $<7.0\%$  (53 mmol/mol) or  $\leq 6.5\%$  (48 mmol/mol) and percentages of patients achieving HbA1c  $<7.0\%$  or  $\leq 6.5\%$  with no hypoglycaemia during the last 12 weeks of treatment. Also assessed were end-of-trial daily insulin dose, changes from baseline in body weight, laboratory-measured fasting plasma glucose (FPG) and blood pressure. Supportive secondary safety endpoints included adverse events (AEs), severe or BG-confirmed symptomatic hypoglycaemic episodes, standard laboratory assessments, clinical evaluations and pulse. Severe or BG-confirmed symptomatic hypoglycaemia was defined as severe (requiring the assistance of another person) or BG-confirmed ( $<56$  mg/dL [ $<3.1$  mmol/L]) hypoglycaemic episodes with symptoms consistent with hypoglycaemia. Severe or BG-confirmed symptomatic hypoglycaemic events with onset between 12:01 AM and 5:59 AM (inclusive) were classified as nocturnal (Figure S2, Appendix S1). Patient-reported outcomes (PROs) were measured using the Treatment-Related Impact Measure for Diabetes (TRIM-D) and Short Form (36) Health Survey (SF-36v2). For TRIM-D, the change-from-baseline score in each of the 5 subdomains (calculated by summing across items in the same domain) and the total score (calculated by adding scores from all domains) were assessed after 32 weeks. For the total score, a higher score indicates a better health status in terms of less negative impact of the treatment in relation to treatment burden, daily life, diabetes management, compliance and psychological health. For SF-36v2, the change-from-baseline score in each of the 8 subdomains and 2 component summary scores (mental health and physical health; calculated by adding scores from their respective subdomains) were assessed after 32 weeks. A higher score indicates better functional health and well-being. A central laboratory (Q<sup>2</sup> Solutions Central Laboratory, Marietta, Georgia) performed laboratory analyses.

## 2.5 | Statistical analyses

The trial was powered for the primary objective of demonstrating non-inferiority with respect to change in HbA1c using a one-sided *t*-test of size 2.5% under the following assumptions: a mean treatment difference of 0.0%, a standard deviation (SD) of 1.0% (11 mmol/mol), a non-inferiority margin of 0.30% (3 mmol/mol), 1:1 randomization and 15% dropout from the per-protocol (PP) analysis set, defined as all patients who did not violate any inclusion/exclusion criteria and who had HbA1c assessments at baseline (screening or randomization) and after at least 12 weeks of exposure. The assumption that 15% of randomized patients would be excluded from the PP analysis set was based on previous findings from the IDegLira phase 3 DUAL clinical program. The non-inferiority margin of 0.30% in HbA1c was selected based on existing US Food and Drug Administration guidance, and is considered the minimal clinically significant change for HbA1c level.<sup>23</sup> Based on these assumptions, the planned sample size was 416 patients, ensuring 80% power for confirming the primary objective in the PP analysis set. Non-inferiority of the IDegLira once-weekly vs twice-weekly titration algorithm for the primary endpoint

was considered confirmed if the 95% confidence interval for the mean treatment difference was entirely below 0.30%.

Analyses of efficacy endpoints were based on the full analysis set (FAS; all randomized patients) and analyses of safety endpoints were based on the safety analysis set (all patients receiving at least 1 dose of trial drug). A standard mixed model for repeated measurement (MMRM) with unstructured covariance matrix was applied to the primary and secondary continuous endpoints. This model produces unbiased estimates when the missing data pattern can be explained by the observed data. The model included treatment, visit, region and previous OAD treatment as fixed factors and the corresponding baseline value as a covariate. Interactions between visit and all factors and covariates were included in the model. Percentages of patients achieving HbA1c targets were analysed by a logistic regression model based on FAS with treatment, region and previous treatment as fixed factors and baseline HbA1c as covariate. Solely descriptive statistics were presented for the number of treatment-emergent severe or BG-confirmed hypoglycaemic episodes resulting from the inherently higher frequency of BG measurements in the twice-weekly titration group.

Non-inferiority for the primary endpoint was to be investigated using 3 pre-specified sensitivity analyses. The primary efficacy analysis based on FAS was to be repeated on: (1) the PP analysis set; (2) the completer analysis set (CAS; all patients who completed the trial); and (3) the FAS with last observation carried forward (LOCF) imputed data using an ANOVA model with treatment, region and previous OAD treatment as fixed factors and baseline HbA1c as covariate.

## 3 | RESULTS

### 3.1 | Patients

Of 613 patients screened, 420 were randomized and 395 completed the trial (Figure S3, Appendix S1). Completion rates were 91% and 97% for once-weekly and twice-weekly titration, respectively. Six patients (2.9%) had AEs leading to withdrawal in the IDegLira once-weekly titration group and 2 patients (1.0%) in the IDegLira twice-weekly titration group. One patient in the IDegLira once-weekly titration group met the withdrawal criterion of exceeding pre-defined fasting SMPG or FPG limits. Treatment groups were well matched with respect to demographic and baseline characteristics (Table 1).

### 3.2 | Glucose control

After 32 weeks of treatment, the observed mean (SD) HbA1c decreased by 2.01% (1.09) [22 mmol/mol (12)] to 6.1% (43 mmol/mol) with once-weekly titration, and by 2.02% (0.98) [22 mmol/mol (11)] to 6.0% (42 mmol/mol) with twice-weekly titration, corresponding to an estimated treatment difference (ETD) of 0.12% [-0.04; 0.28]<sub>95% CI</sub> (1.30 mmol/mol [-0.41; 3.01]<sub>95% CI</sub>) (Figure 1A), confirming non-inferiority of once-weekly compared with twice-weekly titration of IDegLira. The MMRM sensitivity analyses in the PP and CAS

**TABLE 1** Baseline characteristics of patients in each treatment arm of the DUAL VI trial

	IDegLira 1WT	IDegLira 2WT
Full analysis set, n	210	210
Female, %	47	47
Age, years	56.6 (10.3)	57.0 (9.6)
Weight, kg	95.9 (18.9)	95.2 (15.8)
BMI, kg/m <sup>2</sup>	32.4 (4.6)	32.5 (4.4)
Duration of diabetes, years	7.4 (5.6)	7.2 (5.4)
HbA <sub>1c</sub> , % [mmol/mol]	8.2 (0.9) [65.6 (9.3)]	8.1 (0.9) [64.5 (9.4)]
FPG, mmol/L [mg/dL]	10.1 (2.6) [181.9 (47.4)]	10.1 (2.5) [182.1 (44.9)]
Metformin alone (%)	94.3	95.2
Metformin + pioglitazone (%)	5.7	4.8

Values are mean ( $\pm$ SD) unless otherwise stated.

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; IDegLira, insulin degludec/liraglutide; SD, standard deviation; 1WT, once-weekly titration; 2WT, twice-weekly titration.

were in agreement with the primary analysis. When using an ANOVA model based on LOCF-imputed data, however, the 95% CIs exceed the non-inferiority margin (Table S3, Appendix S1).

Consistent with the reduction in HbA<sub>1c</sub>, similar proportions of patients (no significant differences) achieved glycaemic targets and the composite endpoints for HbA<sub>1c</sub> targets with no hypoglycaemia. Similar proportions of patients achieved HbA<sub>1c</sub> targets and composite endpoints for HbA<sub>1c</sub> targets with no hypoglycaemia, with almost 90% of patients in both treatment groups achieving HbA<sub>1c</sub> < 7.0% (Table 2).

Mean (SD) FPG decreased by 78.0 mg/dL (50.7) (4.3 mmol/L [2.8]) with once-weekly titration and by 81.9 mg/dL (46.4) (4.6 mmol/L [2.6]) with twice-weekly titration (ETD: 3.96 mg/dL [-2.02; 9.93]<sub>95% CI</sub>, 0.22 mmol/L [-0.11; 0.55]<sub>95% CI</sub>,  $P = .194$ ), and was similar after 32 weeks (Figure 1B).

Mean daily insulin dose was 11 units at week 1 and increased steadily throughout the trial for both treatment groups. In accordance with the titration regimen, mean insulin dose increased more rapidly in the twice-weekly titration group, but insulin doses were similar between treatment groups by week 21, and the mean IDegLira dose at 32 weeks was 41 dose steps (41 units IDeg and 1.48 mg Lira) for both treatment groups (Figure 1C). Importantly, for each treatment group, the actual and recommended daily doses were similar for each of the two arms (Figure S5, Appendix S1), indicating good overall compliance with titration guidance.

IDegLira was associated with weight loss with both titration algorithms; mean (SD) weight change was -1.0 kg (4.2) for once-weekly vs -2.0 kg (4.9) for twice-weekly titration, corresponding to a statistically significant ETD of 1.09 kg [0.22; 1.96]<sub>95% CI</sub>,  $P = .014$  (Figure 1D).

### 3.3 | Safety endpoints

Severe or BG-confirmed symptomatic hypoglycaemia occurred in 5.7% and 16.2% of patients in the once-weekly and twice-weekly

titration groups, respectively, with rates of 0.16 events/patient-year of exposure (PYE) for once-weekly and 0.76 events/PYE for twice-weekly titration. The mean cumulative plot is shown in Figure 1E. One patient experienced severe hypoglycaemia (IDegLira twice-weekly titration). Rates of nocturnal severe or BG-confirmed symptomatic hypoglycaemia were also low in both groups, and lower with once-weekly titration (Table 3).

The overall AE rates were similar in the IDegLira once-weekly and twice-weekly titration arms (Table 4). The majority of AEs were non-serious, mild in severity and unlikely to be related to trial products, as judged by the investigator; hence, treatment was considered to be well tolerated. The rate of AEs judged to be probably related to trial product was low for both treatment groups: 12.3 vs 11.8 events/100 PYE for once-weekly vs twice-weekly titration of IDegLira, respectively, with the most common AEs considered possibly or probably related to trial product being nausea, constipation, diarrhoea, increased lipase and headaches. Overall, these AEs occurred with similar frequency in both treatment groups. The only AEs to occur in  $\geq 5\%$  of patients were nausea (5.3% vs 5.2% of patients in once-weekly vs twice-weekly titration groups) and nasopharyngitis (6.2% vs 4.3% of patients in once-weekly vs twice-weekly titration groups). The rates of serious AEs were low (Table 4), with no obvious pattern in type of events, and no single type of serious AE occurred in  $\geq 1\%$  of patients. There were no differences in pulse rate or diastolic or systolic blood pressure between treatment groups (Table S4, Appendix S1).

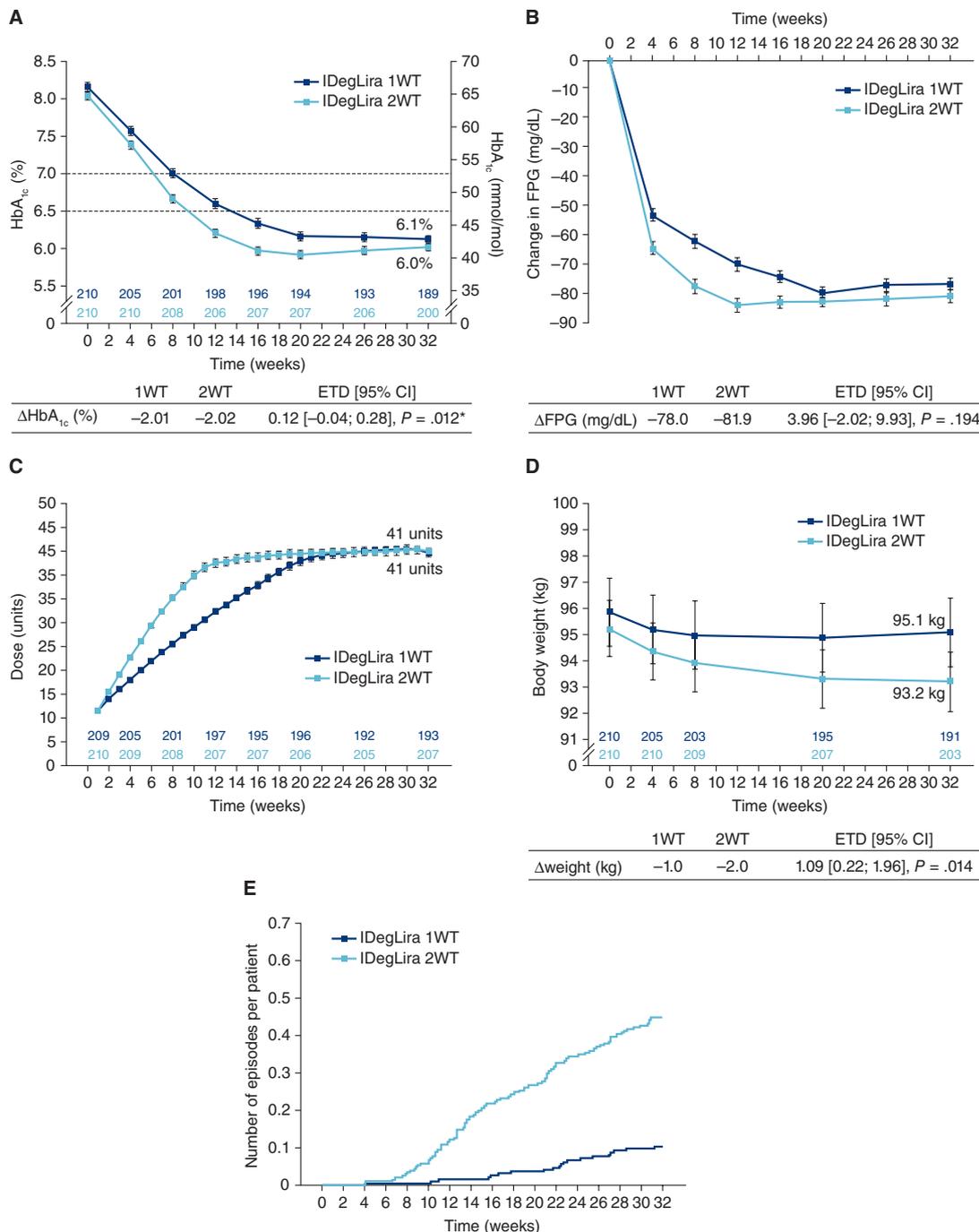
There was one confirmed adjudicated major adverse cardiovascular event (MACE) in each treatment group (myocardial infarction in the once-weekly titration group and a fatal event in the twice-weekly titration group). There were 3 confirmed adjudicated neoplasm events, only one of which was malignant (female reproductive).

### 3.4 | Patient-reported outcomes

There was no significant difference between the 2 titration algorithms in improvement of TRIM-D total score or any TRIM-D subdomain score, or of physical component score and subdomains of the SF-36v2 questionnaire. Patients in the IDegLira once-weekly titration group reported significantly greater improvements than patients using the twice-weekly titration algorithm in the vitality, social functioning and mental health subdomain scores of the mental health component of the SF-36v2 questionnaire (all  $P < .05$ ). There was no statistically significant treatment difference for overall mental score of SF-36v2 (Figure S4, Appendix S1).

## 4 | DISCUSSION

This 32-week, open-label, non-inferiority trial investigated the efficacy and safety of a pragmatic once-weekly titration algorithm for IDegLira vs the twice-weekly titration algorithm used in prior DUAL trials. The once-weekly titration algorithm was non-inferior to the twice-weekly titration algorithm, with HbA<sub>1c</sub> decreasing to similar values at end of trial. This was confirmed by the sensitivity analyses, with the exception of the sensitivity analysis based on LOCF imputed



**FIGURE 1** A, HbA<sub>1c</sub> over time with IDegLira once-weekly vs twice-weekly titration. Mean observed values with error bars (standard error mean) based on FAS. Treatment difference analysed using MMRM based on FAS. \*Test against non-inferiority limit of 0.3%. --- ADA/EASD HbA<sub>1c</sub> target < 7.0%; AACE HbA<sub>1c</sub> target ≤ 6.5%. B, Change in FPG from baseline. LS Mean values with error bars (standard error mean) based on FAS (IDegLira 1WT/IDegLira 2WT: n = 210/210), using MMRM. C, Daily insulin dose over time. Mean observed values with error bars (standard error mean) based on SAS. D, Body weight over time. Mean observed values with error bars (standard error mean) based on FAS. Treatment difference analysed using MMRM based on FAS. E, Severe or BG-confirmed symptomatic hypoglycaemia. Mean cumulative function based on SAS (IDegLira 1WT/IDegLira 2WT: n = 209/210). Because of the study design, with more SMPG measurements taken in the 2WT group, the number of hypoglycaemic episodes is expected to be biased towards more hypoglycaemic episodes in the 2WT group compared with the 1WT group. Hence, solely descriptive analysis was applied. The MMRM model included treatment, visit, region and previous OAD treatment as factors, and baseline value as covariate. Interactions between visit and all other factors and the covariate are also included in the model. AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association; BG, blood glucose; EASD, European Association for the Study of Diabetes; ETD, estimated treatment difference; FAS, full analysis set; FPG, fasting plasma glucose; IDegLira, insulin degludec/liraglutide; LS Mean, least square mean; MMRM, mixed model for repeated measurement; OAD, oral antidiabetic drug; SAS, safety analysis set; SMPG, self-measured plasma glucose; 1WT, once-weekly titration; 2WT, twice-weekly titration.

**TABLE 2** Proportion of patients achieving HbA1c targets and composite endpoints

	Proportion of patients (%)			
	IDegLira 1WT	IDegLira 2WT	Odds ratio IDegLira 1WT/2WT	
			Estimate	[95% CI]
HbA1c < 7%	89.9	89.5	0.95	[0.51; 1.78]
HbA1c < 7%, no hypoglycaemic episodes <sup>1</sup>	85.7	83.5	1.14	[0.66; 1.96]
HbA1c ≤ 6.5%	83.6	85.0	0.88	[0.52; 1.49]
HbA1c ≤ 6.5%, no hypoglycaemic episodes <sup>1</sup>	79.4	79.0	1.02	[0.63; 1.66]

Odds ratios are from a logistic regression model based on FAS using logit link with treatment, region and previous OAD treatment as fixed factors, and baseline HbA1c as covariate.

Abbreviations: BG, blood glucose; CI, confidence interval; FAS, full analysis set; IDegLira, insulin degludec/liraglutide; OAD, oral antidiabetic drug; 1WT, once-weekly titration; 2WT, twice-weekly titration.

<sup>1</sup> Severe or BG-confirmed symptomatic hypoglycaemia is based on hypoglycaemic episodes during a patient's last 12 weeks of treatment.

**TABLE 3** Rates of hypoglycaemia by definition and classification

	IDegLira 1WT				IDegLira 2WT			
	n	%	E	R	n	%	E	R
Severe	0				1	0.5	1	0.8
Severe or BG-confirmed symptomatic	12	5.7	20	16.4	34	16.2	97	76.2
Severe or BG-confirmed	18	8.6	35	28.8	50	23.8	138	108.4
Nocturnal severe or BG-confirmed symptomatic	2	1.0	2	1.6	14	6.7	29	22.8
Nocturnal severe or BG-confirmed	4	1.9	4	3.3	15	7.1	32	25.1

Data based on safety analysis set. Nocturnal was defined as between 12:01 AM and 5:59 AM (both inclusive).

Abbreviations: BG, blood glucose; E, number of events; IDegLira, insulin degludec/liraglutide; n, number of patients with at least 1 event; R, rate of events per 100 patient-years of exposure; %, percentage of patients; 1WT, once-weekly titration; 2WT, twice-weekly titration.

values. This is probably caused by the fact that there were more patients who withdrew before week 12 in the IDegLira once-weekly titration group compared with the twice-weekly titration group. FPG reductions and proportion of patients achieving HbA1c targets and composite endpoints were also similar between treatment groups. The final mean HbA1c of approximately 6%, achieved in both groups, represents exceptionally good glycaemic control. That this was achieved tolerably with both titration algorithms, with similar FPG reductions and low risk of hypoglycaemia supports the use of either titration regimen in clinical practice.

Daily IDegLira dose was 41 dose steps at end of trial for both treatment groups. However, with twice-weekly titration, a near maximal dose was reached after 12 weeks, whereas insulin dose did not

**TABLE 4** Summary of treatment-emergent adverse events

	IDegLira 1WT (n = 209)	IDegLira 2WT (n = 210)
Number of patients	103	106
Percentage of patients	49.3	50.5
Number of events	253	307
Adverse event rate per 100 PYE	207.8	241.3
Serious adverse event rate per 100 PYE	8.2	13.4

Data based on safety analysis set. There was 1 event of myocardial infarction (1WT) and 1 event of CV death (2WT). One malignant female reproductive event and 1 benign colorectal event were confirmed in the 1WT group, and 1 benign head and neck event was confirmed in the 2WT group. There were no confirmed thyroid or pancreatitis events.

Abbreviations: CV, cardiovascular; IDegLira, insulin degludec/liraglutide; PYE, patient-year of exposure; 1WT, once-weekly titration; 2WT, twice-weekly titration.

begin to plateau until approximately week 21 in the once-weekly titration group (Figure 1C). Both titration algorithms were associated with weight loss; however, significantly greater weight loss was observed with twice-weekly vs once-weekly titration. Reasons for this treatment difference are possibly related to the slightly accelerated increase in liraglutide exposure with once-weekly vs twice-weekly titration during the titration phase, resulting in faster weight loss with twice-weekly titration. Nevertheless, the observation that glycaemic control can be achieved without weight gain with IDegLira in previously insulin-naïve patients is consistent with results from DUAL I, in which there was a mean weight reduction (using LOCF-imputed data) of 0.5 kg in the IDegLira treatment arm.

Rates of severe or blood glucose-confirmed symptomatic hypoglycaemia were low for both titration algorithms. The greater divergence in the curves observed during weeks 6 to 16 (Figure 1E) may be related to the discrepancy in drug exposure between the 2 titration groups. Nevertheless, even from week 22 onwards, when both groups had reached final dose, there still appeared to be a divergence in the hypoglycaemia curves. This is probably an artefact attributable to the more frequent BG monitoring in the twice-weekly titration group.

In general, IDegLira was well-tolerated when added to treatment with metformin ± pioglitazone. There were few different types of AEs reported for IDegLira and they were no different from what was expected from its mono-components – insulin degludec and liraglutide.<sup>16,24,25</sup>

Patients often cite the expected impact of burdensome regimens on quality of life as a barrier to insulin initiation/intensification,<sup>4,5</sup> and results from the AT.LANTUS<sup>19</sup> and INSIGHT<sup>20</sup> studies have suggested that simple titration algorithms can do much to tackle this barrier. Furthermore, a pooled analysis of patient-level data from prospective, randomized, controlled clinical trials demonstrated that simpler, patient-managed basal insulin titration algorithms achieved similar glycaemic control, but with less hypoglycaemia as compared to physician-managed titration algorithms.<sup>26</sup> Based on this, one would expect that treatment burden would be less with IDegLira titrated once weekly, and the results from the PROs seem to support this assumption. The SF-36 subdomains of Vitality, Social functioning and Mental health were significantly higher in favour of once-weekly

titration. There was no significant difference in the Compliance and Treatment burden subdomains of TRIM-D. Nevertheless, both treatment arms benefited from improvements in PROs, and a substantial difference between the titration groups might not be expected, given that large proportions of patients in each treatment arm achieved HbA1c targets with no hypoglycaemia. However, these results do suggest that patients who have resisted insulin initiation thus far, because they believe it will greatly impact their quality of life, might prefer initiation of IDegLira using once-weekly titration. The once-weekly titration algorithm might also have the advantage of reduced healthcare costs as a result of the fewer number of BG test strips required. This, together with a titration algorithm that can be patient-managed, might make IDegLira a more attractive option earlier on in a patient's disease trajectory, thereby facilitating the adoption of an approach aimed at addressing the underlying pathophysiology. This approach is particularly important in primary care because the earlier in the progression of disease this approach is introduced, the greater the impact it can have on slowing progressive beta-cell failure.<sup>27,28</sup> Therefore, the development and evaluation of simple titration algorithms, such as the one described here for IDegLira, is of great importance.

An inherent limitation of randomized controlled trials is that the clinical applicability of the results is limited to those who fit the inclusion and exclusion criteria and the settings in which they were assessed. In this case, patients were to be able and willing to adhere to the protocol and they were then advised on the importance of adhering to trial protocol at every visit with the investigator. The extent to which this will differ from clinical practice is unclear, but the results demonstrate that either titration regimen can be employed safely and effectively in insulin-naïve patients with T2D uncontrolled on OADs.

In conclusion, a pragmatic IDegLira titration algorithm with once-weekly dose adjustments based on 2 PG readings resulted in a safety and glycaemic efficacy profile similar to that with twice-weekly adjustments based on 3 preceding PG values.<sup>13,14</sup> This pragmatic titration algorithm can therefore be considered on an individual basis for insulin-naïve patients uncontrolled on OADs.

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## Conflicts of interest

S. B. H. received consulting and advisory board honoraria from Sanofi, Lilly, Novo Nordisk, Janssen, Merck, Takeda, Boehringer

Ingelheim, Bristol-Myers Squibb and AstraZeneca; lecture honoraria from Sanofi, Novo Nordisk, Lilly, AstraZeneca and Merck; and funds were given to his institution for research or educational initiatives by Sanofi, Merck, and Novo Nordisk. G. K. has participated in an advisory panel for Novo Nordisk and acted as consultant for, and received research support from, Medtronic. R. P. has participated in advisory panels for Novo Nordisk, Eli Lilly, Merck Sharp and Dohme, Sanofi Aventis, and Boehringer Ingelheim. T. R. has participated in advisory panels for Novo Nordisk and Sanofi; received research support from Novo Nordisk, Sanofi, Eisai, Novartis, Merck, Takeda, Eli Lilly and Co.; and participated in speakers' bureaus for Janssen and Novo Nordisk. K. C. and N. H. are employees and stock/shareholders of Novo Nordisk. S. J. has participated in speakers' bureaus for, and received research support from, Lilly, Janssen and AstraZeneca.

## Author contributions

S. B. H. 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 and the accuracy of the data analysis. All authors (S. B. H., G. K., R. P., T. R., K. C., N. H. and S. J.) confirm that they meet the International Committee of Medical Journal Editors (ICJME) uniform requirements for authorship and that they have contributed to critical analysis and interpretation of the data, drafting and/or critically revising the article and sharing in the final responsibility for the content of the manuscript and the decision to submit it for publication.

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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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