

## Research: Treatment

# Safety and efficacy of insulin degludec/liraglutide (IDegLira) added to sulphonylurea alone or to sulphonylurea and metformin in insulin-naïve people with Type 2 diabetes: the DUAL IV trial

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### Abstract

**Aim** To investigate the safety and efficacy of insulin degludec/liraglutide (IDegLira), a novel combination product, as add-on therapy for people with Type 2 diabetes uncontrolled on sulphonylurea therapy.

**Methods** In this 26-week, double-blind trial, adults with Type 2 diabetes [HbA<sub>1c</sub> 53–75 mmol/mol (7.0–9.0%)] were randomized to IDegLira ( $n = 289$ ) or placebo ( $n = 146$ ) as add-on to pre-trial sulphonylurea  $\pm$  metformin, titrating to a fasting glycaemic target of 4.0–6.0 mmol/l. Treatment initiation was at 10 dose steps, and maximum dose was 50 dose steps (50 units insulin degludec/1.8 mg liraglutide).

**Results** The mean HbA<sub>1c</sub> decreased from 63 mmol/mol (7.9%) to 46 mmol/mol (6.4%) with IDegLira and to 57 mmol/mol (7.4%) with placebo [estimated treatment difference  $-11$  mmol/mol (95% CI  $-13$ ;  $-10$ ) or  $-1.02\%$  (95% CI  $-1.18$ ;  $-0.87$ );  $P < 0.001$ ]. The HbA<sub>1c</sub> target of 53 mmol/mol ( $<7\%$ ) was achieved by 79.2% of participants in the IDegLira group vs 28.8% in the placebo group [estimated odds ratio 11.95 (95% CI 7.22; 19.77);  $P < 0.001$ ]. Mean weight change was  $+0.5$  kg with IDegLira vs  $-1.0$  kg with placebo [estimated treatment difference 1.48 kg (95% CI 0.90; 2.06);  $P < 0.001$ ]. Confirmed hypoglycaemia occurred in 41.7 and 17.1% of IDegLira- and placebo-treated participants, respectively, with rates of 3.5 vs 1.4 events/patient-years of exposure [estimated rate ratio 3.74 (95% CI 2.28; 6.13);  $P < 0.001$ ]. IDegLira was generally well tolerated. The rates of serious adverse events were 20.3 and 8.0 per 100 patient-years of exposure with IDegLira and placebo, respectively, without obvious patterns in the type of events.

**Conclusions** IDegLira can be used in people uncontrolled with sulphonylurea  $\pm$  metformin to improve efficacy with a safety profile in line with previous DUAL trials.

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### Introduction

Metformin and sulphonylureas are the most popular choices of Type 2 diabetes treatment [1–3], with approximately one-fifth of people being treated with sulphonylureas [4]. Although many clinicians prefer to discontinue sulphonylurea use on initiation of basal insulin therapy because of an increased risk of hypoglycaemia [1,5,6], many people

continue to receive sulphonylureas in combination with basal insulin therapy [4].

The glucagon-like peptide 1 (GLP-1) receptor agonists stimulate insulin secretion and suppress glucagon release in a glucose-dependent manner [7], and are associated with weight loss and a low risk of hypoglycaemia, but may cause transient gastrointestinal side effects [8–12]. Regimens in which GLP-1 receptor agonists are added to basal insulins, or vice versa, have been shown to be effective and well tolerated in several trials [13,14].

IDegLira is a novel once-daily combination product of insulin degludec, a basal insulin and liraglutide, a GLP-1 receptor agonist, developed for the treatment of Type 2

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**What's new?**

- IDegLira is a combination of insulin degludec and liraglutide. Basal insulins and glucagon-like peptide-1 (GLP-1) receptor agonists have complementary effects in a Type 2 diabetes treatment regimen, with GLP-1 receptor agonists also being insulin-sparing.
- Treatment guidelines often advocate discontinuing sulphonylureas on basal insulin initiation, but widespread concomitant use of these drugs continues in current clinical practice. It is therefore anticipated that many sulphonylurea-treated people will have IDegLira added to their therapy, yet this combination has not previously been studied
- This randomized controlled trial shows that IDegLira can be used in people uncontrolled with sulphonylureas ± metformin to improve efficacy with a favourable benefit–risk profile.

diabetes [15,16]. The phase IIIa trial DUAL I [15,17] showed that IDegLira improved glycaemic control compared with its individual components given alone, with a low rate of hypoglycaemia, nausea and weight gain in insulin-naïve people uncontrolled on oral antidiabetic drugs. As it is likely that many people will be prescribed IDegLira in combination with their current sulphonylurea therapy, the aim of the present study was to examine the safety and efficacy of IDegLira in insulin-naïve people uncontrolled on sulphonylureas with or without metformin.

**Materials and methods****Study design and participants**

This phase III, 26-week, randomized, double-blind, parallel-group trial was conducted at 77 sites in seven countries (Table S1) between August 2012 and October 2013. 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 [18] and International Conference on Harmonisation Good Clinical Practice guidelines [19]. Eligible participants were adults (age ≥18 years) with Type 2 diabetes, HbA<sub>1c</sub> levels of 53–75 mmol/mol (7.0–9.0%, both inclusive) and BMI of ≤40 kg/m<sup>2</sup>, previously treated with a stable daily dose of sulphonylureas (≥half of the maximum approved dose according to local label) ± metformin (≥1500 mg or maximum tolerated dose) for at least 90 days before screening. Participants were insulin- and GLP-1 receptor agonist-naïve, and were excluded if they had been treated with any antidiabetic agent other than sulphonylureas or

metformin for ≤90 days before screening (Table S2 shows the inclusion and exclusion criteria).

**Randomization and masking**

Participants were randomized using a central interactive voice/web system in a 2:1 ratio to receive once-daily, subcutaneous injections of either IDegLira (100 units/ml insulin degludec and 3.6 mg/ml liraglutide, 3 ml prefilled pen; Novo Nordisk, Bagsværd, Denmark) or placebo. The placebo solution was identical to the vehicle used for IDegLira. Novo Nordisk ensured continuous safety surveillance and monitoring of titration. An external independent event adjudication committee performed ongoing adjudication and assessment of selected events. An independent committee of thyroid experts monitored increased calcitonin levels. Treatment was masked for investigators and participants by use of the PDS290 pen-injector to administer either IDegLira or placebo. Masking was maintained for the participants and all personnel involved in the trial (including titration, event adjudication and calcitonin monitoring) until the database was locked and released for statistical analyses.

**Procedures**

Sulphonylureas and metformin were maintained at pre-trial dose and frequency unless there was a safety concern. Counselling regarding healthy lifestyle and exercise was provided for all participants during the trial. At randomization, IDegLira or placebo was initiated at 10 dose steps. One dose step of IDegLira contains 1 unit insulin degludec and 0.036 mg liraglutide. Doses of IDegLira or placebo were adjusted twice per week according to a predefined titration algorithm (Table S3), based on the mean fasting pre-breakfast self-monitored blood glucose (SMBG) measurements, from 3 consecutive days, aiming to achieve a mean pre-breakfast blood glucose concentration of 4.0–6.0 mmol/l (72–108 mg/dl). IDegLira or placebo was administered once daily, independent of meals but preferably at the same time each day. The maximum allowed doses were 50 dose steps for IDegLira (50 U insulin degludec and 1.8 mg liraglutide) and 50 dose steps of placebo. Participants performed blood glucose monitoring with a glucose meter [Abbott Diabetes Care, Abbott Park, USA; model dependent on local availability (Table S4)], calibrated to plasma values; meters were used according to the manufacturer's instructions.

**Outcome measures**

The primary endpoint was change from baseline in HbA<sub>1c</sub> after 26 weeks of treatment. Secondary efficacy endpoints included the percentages of participants with end-of-trial HbA<sub>1c</sub> of <53 mmol/mol (7.0%) or ≤48 mmol/mol (6.5%), changes in body weight, laboratory-measured fasting plasma glucose and nine-point SMBG profiles. Safety endpoints

included adverse events, hypoglycaemic episodes, standard laboratory assessments, clinical evaluations and vital signs. Confirmed hypoglycaemic episodes were defined as those requiring the assistance of another person (severe) and/or those with a plasma glucose value  $<3.1$  mmol/l ( $<56$  mg/dl), regardless of symptoms. Confirmed hypoglycaemia with onset between 00:01 and 05:59 h (both inclusive) was classified as nocturnal. A serious adverse event was defined as an event that at any dose resulted in either death, a life-threatening experience, hospitalization (or extension thereof), a persistent or significant disability/incapacity, a congenital anomaly or an important medical event that, based on appropriate medical judgement, could have jeopardized the participant and required medical intervention to prevent one of the outcomes listed in this definition. A non-serious adverse event was any adverse event that did not fulfil the definition of a serious adverse event. It was at the discretion of the investigator to evaluate if the event was a serious adverse event or a non-serious event. A central laboratory (Quintiles Ltd, Livingston, UK) performed laboratory analyses.

### Statistical analyses

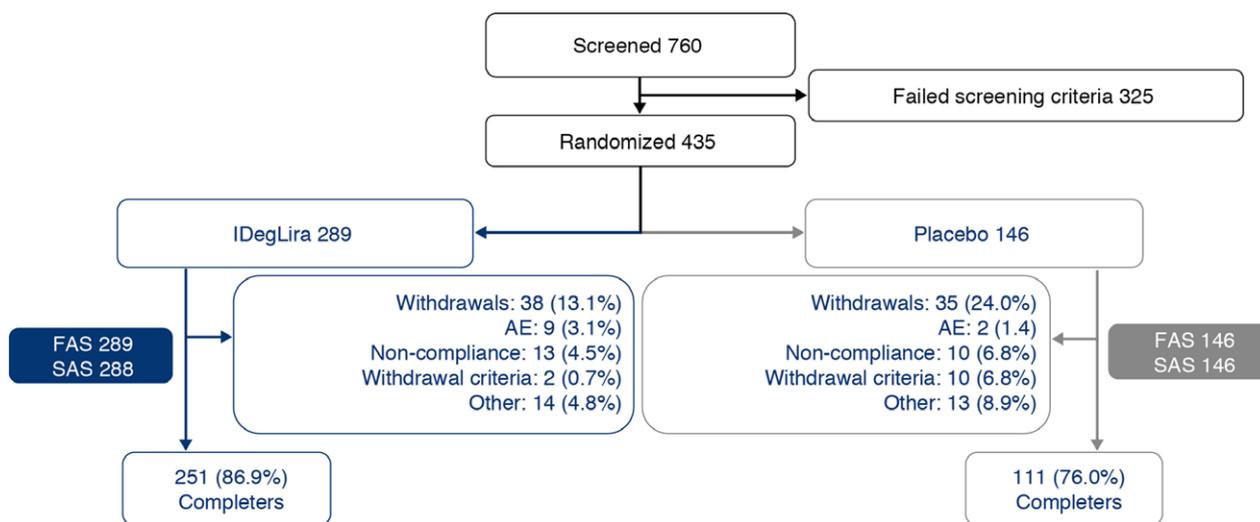
The primary objective was to confirm the superiority of IDegLira vs placebo with respect to change in HbA<sub>1c</sub> from baseline after 26 weeks of treatment. Sample size was calculated using a two-sided *t*-test, with an  $\alpha$  value of  $P = 0.05$ , assuming a mean treatment difference (IDegLira–placebo) of  $-4$  mmol/mol ( $-0.4\%$ ) and a standard deviation (SD) of  $1.2\%$  ( $13$  mmol/mol) for HbA<sub>1c</sub>. To obtain a nominal power of  $90\%$ , 429 participants were to be randomized. The primary endpoint was analysed using an analysis of covariance (ANCOVA) model with treatment, geographical region and pre-trial medication as fixed factors, and baseline HbA<sub>1c</sub>

as covariate. This analysis was carried out on the full analysis set using last observation carried forward (LOCF) to impute missing values. Superiority of IDegLira vs placebo was to be confirmed if the  $95\%$  CIs for treatment difference in change of HbA<sub>1c</sub> was  $< 0\%$ . Sensitivity analyses were performed for the primary endpoint (Table S5). Change from baseline in fasting plasma glucose, body weight and mean nine-point SMBG profile were analysed separately using ANCOVA similar to that used for the primary endpoint. The categorical variables of attaining HbA<sub>1c</sub>  $<53$  mmol/mol ( $7.0\%$ ) or  $\leq 48$  mmol/mol were analysed separately using a logistic regression model (with LOCF), with the same explanatory variables as used for the primary endpoint. A *post hoc* statistical analysis of the nine-point SMBG profile was conducted for each time point with a mixed-effect model using an unstructured residual covariance matrix. The model included treatment, time point, previous antidiabetic treatment, region and treatment by time point interaction as fixed factors and baseline nine-point profile value as covariate. The number of confirmed hypoglycaemic episodes was analysed for the full analysis set using a negative binomial regression model with treatment, geographical region and pre-trial medication as fixed factors and log of the duration of treatment-emergent time period (on/after the first day of treatment and no later than 7 days after the last day of treatment) as offset. Descriptive statistics were presented for the number of treatment-emergent adverse events.

## Results

### Participants

Of 760 participants screened, 435 were randomized and 362 completed the trial (Fig. 1). A lower proportion of participants withdrew from the IDegLira group vs placebo; the



**FIGURE 1** Participant disposition. AE, adverse event; FAS, full analysis set; SAS, safety analysis set.

completion rates were 87% for IDegLira and 76% for placebo. Eleven participants (2.5%) had adverse events leading to withdrawal; nine participants (3.1%) in the IDegLira group and two participants (1.4%) in the placebo group. Withdrawal because of ineffective therapy was more pronounced in the placebo group: one participant receiving IDegLira vs 10 participants receiving placebo. Treatment groups were well matched with respect to demographics and baseline characteristics (Table 1). The proportion of participants receiving the sulphonylureas glibenclamide, gliclazide, glimepiride or glipizide, with mean daily doses at screening, are shown in Table S6.

### Glucose control

Mean (sd) HbA<sub>1c</sub> decreased from 63 (6.4) mmol/mol [7.9 (0.6)%] by 16 (9.2) mmol/mol 1.5 (0.8)% to 47 (8.8) mmol/mol [6.4 (0.8)%] with IDegLira and from 63 (6.4) mmol/mol [7.9 (0.6)%] by 5 (9.1) mmol/mol [0.5 (0.8)%] to 58 (9.4) mmol/mol [7.4 (0.9)%] with placebo, confirming the superiority of IDegLira relative to placebo [estimated treatment difference (ETD) IDegLira – placebo: –11 mmol/mol (95% CI –13; –10) or –1.02% (95% CI –1.18; –0.87);  $P < 0.001$ ].

**Table 1** Baseline characteristics of study participants

	IDegLira	Placebo
Full analysis set, <i>n</i>	289	146
Male/female, %	53.3/46.7	50.0/50.0
Race, %		
White	75.1	76.0
Black or African-American	5.5	8.9
Asian	18.0	13.7
Other	1.4	1.4
Ethnicity: Hispanic or Latin American, %	24 (8.3)	16 (11.0)
Age, years	60.0 (9.6)	59.4 (10.8)
Weight, kg	87.2 (18.6)	89.3 (17.5)
BMI, kg/m <sup>2</sup>	31.2 (4.8)	32.0 (4.5)
Waist circumference, cm	106.4 (13.5)	105.9 (12.7)
Duration of diabetes, years	9.0 (5.5)	9.3 (6.5)
HbA <sub>1c</sub>		
mmol/mol	63 (6)	63 (6)
%	7.9 (0.6)	7.9 (0.6)
Fasting plasma glucose		
mmol/l	9.1 (2.2)	9.1 (2.1)
mg/dl	164.4 (38.9)	164.7 (37.5)
Lipid profile, mmol/l		
Total cholesterol	4.48 (1.05)	4.57 (1.11)
HDL cholesterol	1.18 (0.30)	1.16 (0.32)
LDL cholesterol	2.39 (0.87)	2.49 (0.95)
VLDL cholesterol	0.89 (0.45)	0.91 (0.41)
Blood pressure, mmHg		
Systolic	132.5	132.4
Diastolic	78.3	78.9
Urinary albumin-to-creatinine ratio at visit 1, mg/mmol	9.4 (30.8)	5.1 (11.7)
Oral antidiabetic drugs at screening		
Sulphonylurea	10.4	11.6
Sulphonylurea + metformin	89.6	88.4

Data based on full analysis set. Values are mean (sd) unless otherwise stated.

(Fig. 2a)]. Three prespecified sensitivity analyses led to the same conclusion and showed the robustness of the primary analysis (Table S5). A greater proportion of IDegLira-treated participants achieved glycaemic targets; 79.2% of IDegLira participants reached HbA<sub>1c</sub> ≤53 mmol/mol (<7%) compared with 28.8% of participants receiving placebo, with an estimated odds ratio of 11.95 (95% CI 7.22; 19.77;  $P < 0.001$ ). Similarly, HbA<sub>1c</sub> ≤48 mmol/mol (6.5%) was achieved by 64.0% of IDegLira participants compared with 12.3% receiving placebo, with an estimated odds ratio of 16.36 (95% CI 9.05; 29.56;  $P < 0.001$ ). Change in laboratory-measured fasting plasma glucose was significantly greater for participants receiving IDegLira vs placebo: –2.60 (2.61) mmol/l vs –0.31 (2.43) mmol/l, respectively, with an ETD of –2.30 mmol/l [95% CI –2.72; –1.89;  $P < 0.001$  (Fig. 2b)]. The greatest change in fasting plasma glucose in both treatment groups was observed during the first 4 weeks of treatment, with a much larger change for IDegLira than for placebo.

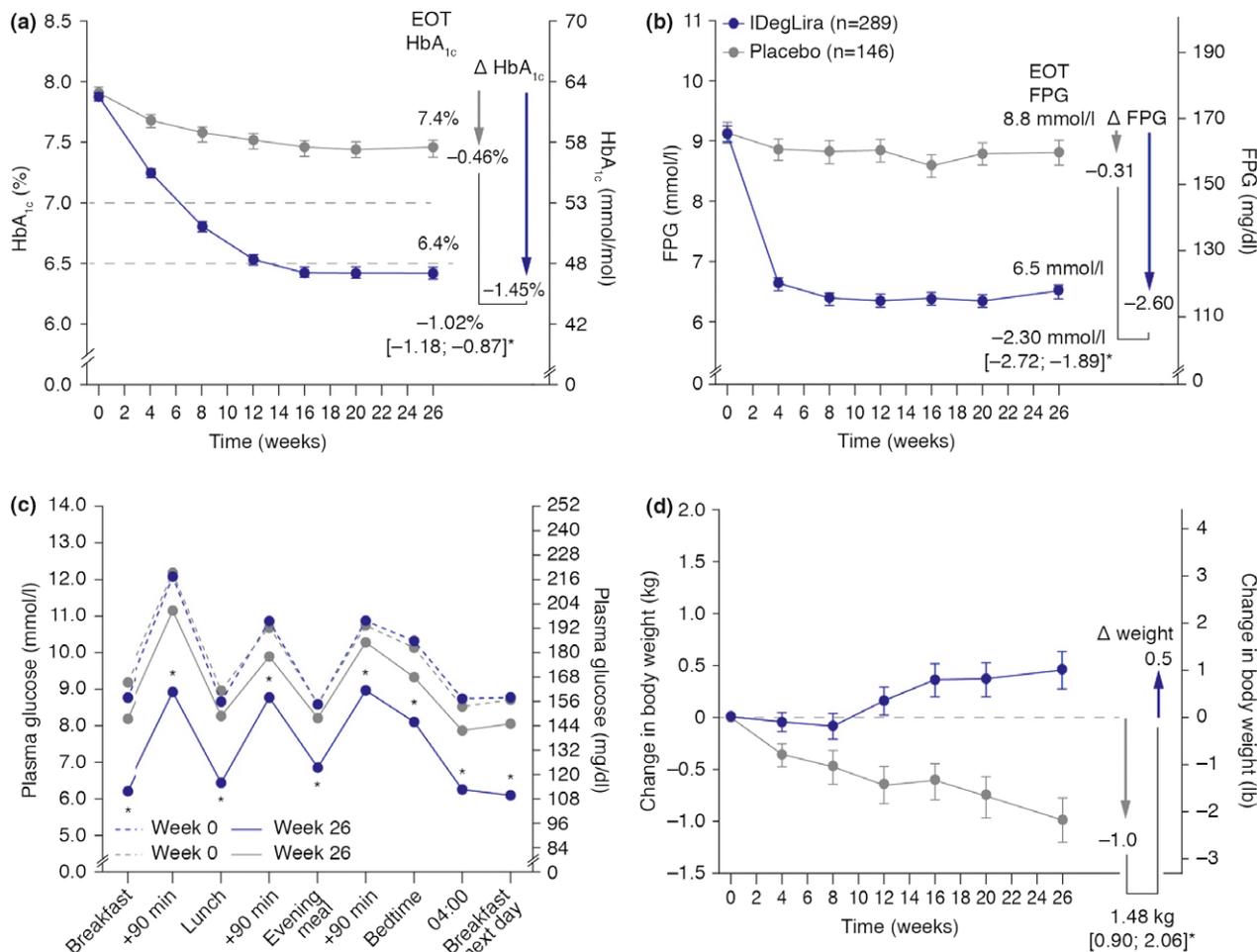
Mean nine-point SMBG profiles at baseline and week 26 are shown in Fig. 2c. The profiles for the IDegLira and placebo groups were similar at baseline. The mean (sd) reduction in mean nine-point SMBG was 2.2 mmol/l (2.1) for IDegLira vs 0.7 (1.7) mmol/l for placebo, with an estimated treatment difference of –1.55 mmol/l (95% CI –1.86; –1.24;  $P < 0.001$ ). Blood glucose levels were significantly lower with IDegLira at all nine time-points (*post hoc* analysis; Fig. 2c). There were no statistically significant differences in the change from baseline (sd) in prandial glucose increments relative to baseline between the IDegLira group and the placebo group [–0.3 (2.0) mmol/l and –0.1 (2.0) mmol/l, respectively; ETD 0.04 mmol/l (95% CI –0.28; 0.35);  $P = 0.819$ ].

At the end of the trial, the mean dose of IDegLira was 28 dose steps, corresponding to 28 units insulin degludec and 1.0 mg liraglutide, and the mean dose of placebo was 44 dose steps.

There was an increase in mean body weight of 0.5 kg from 87.2 kg at baseline in IDegLira-treated participants and a decrease in mean body weight of –1.0 kg from 89.3 kg at baseline in participants receiving placebo, with an ETD of 1.48 kg [95% CI 0.90; 2.06;  $P < 0.001$  (Fig. 2d)].

### Safety endpoints

Confirmed hypoglycaemia occurred in 41.7 and 17.1% of IDegLira- and placebo-treated participants, respectively, with rates of 3.52 vs 1.35 events per patient-years of exposure [PYE; estimated rate ratio: 3.74 (95% CI 2.28; 6.13);  $P < 0.001$  (Table 2)]. Two events of severe hypoglycaemia occurred during the trial, both in the IDegLira group. Nocturnal confirmed hypoglycaemia occurred at rates of 0.49 and 0.32 events per PYE in the IDegLira and placebo groups, respectively [estimated rate ratio: 2.22 (95% CI 0.99; 5.00);  $P = 0.053$ ].



**FIGURE 2** (a) Glycaemic efficacy (HbA<sub>1c</sub>) over time. Mean observed values with error bars (SEM) based on full analysis set (FAS) and last observation carried forward (LOCF) imputed data. Treatment difference estimated using an ANCOVA model. --- American Diabetes Association/European Association for the Study of Diabetes HbA<sub>1c</sub> target <7.0%; American Association of Clinical Endocrinologists HbA<sub>1c</sub> target ≤6.5%. Estimated treatment difference (ETD [95% CI]); \**P* < 0.001. (b) Fasting plasma glucose (FPG) over time. Mean observed values with error bars (SEM) based on FAS and LOCF imputed data. Treatment difference estimated using an ANCOVA model. ETD [95% CI], \**P* < 0.001. (c) Nine-point self-monitored blood glucose profile. Mean observed values based on FAS and LOCF imputed data. \**P* < 0.05 based on linear mixed model with an unstructured residual covariance matrix. (d) Change in body weight. Mean observed values with error bars (SEM) based on FAS and LOCF imputed data. Treatment difference estimated using an ANCOVA model. ETD [95% CI], \**P* < 0.001. EOT, end of trial.

**Table 2** Confirmed hypoglycaemia

	IDegLira				Placebo				<i>P</i>
	<i>N</i>	%	Number of events	Events per PYE	<i>N</i>	%	Number of events	Events per PYE	
Severe	Overall	2	0.7	2	0.015	–	–	–	–
Confirmed	Overall	120	41.7	467	3.517	25	17.1	84	1.352
	Nocturnal	34	11.8	65	0.490	10	6.8	20	0.322

PYE, patient-years of exposure.

Data based on safety analysis set. Estimated treatment ratios are from a negative binomial model.

%, percentage of participants; *N*, number of participants with ≥1 event.

Treatments were well tolerated, with overall adverse event rates similar in the IDegLira and placebo arms (401.4 vs 367.0 events per 100 PYE, respectively). The majority of adverse events were non-serious, mild in severity, transient

in duration and unlikely to be related to trial products as judged by the investigator. The rate of adverse events judged to be probably related to trial product was higher in the IDegLira group than in the placebo group; 34.6 vs 29.0

events per 100 PYE, respectively (Table S7). Rates of diarrhoea, nausea and vomiting were similar (Table S8): < 2% of participants experienced nausea during any given week of the trial in either group (Fig. S1). The rise in the proportion of participants with nausea in the placebo arm at week 27 shown in Fig. S1 is attributable to the reduced number of ‘participants at risk’ at the very end of the trial. Accordingly, the single event of nausea in the placebo arm at the end of the trial amongst 36 participants shows an increase in proportion. The most common adverse events were increased lipase levels, nasopharyngitis, dyslipidaemia, headache and influenza (Table 3). The only adverse events that occurred with a higher frequency in the IDegLira than in the placebo group were increased lipase levels and dyslipidaemia (Table 3). Of the 25 events of dyslipidaemia, 17 events were reported from one clinical site, and 18 events had an observed onset on day 1 of the trial, before the first dose of trial drug. The rate of serious adverse events was higher in the IDegLira group than in the placebo group (20.3 and 8.0 events per 100 PYE) without any obvious patterns in the type of events (Table S9). No single category of serious adverse event occurred in  $\geq 1\%$  of participants. One severe confirmed hypoglycaemic event in an IDegLira participant (of the two events in total, both in IDegLira arm) was classified as a serious adverse event by the investigator. The higher rate of serious adverse events in the IDegLira arm was driven by two participants who experienced seven and four serious adverse events, respectively. These 11 serious adverse events were all considered to be unlikely to be related to the trial product, IDegLira, by the investigator. There was a mean increase of 11.6 units/l from baseline to end of IDegLira treatment in lipase activity, whereas a decrease of 3.1 units/l was observed in the placebo group. There was also a similar but less pronounced mean increase of 6.7 units/l in amylase activity in the IDegLira-treated group at week 26 compared with a decrease of 2.0 units/l in the placebo group.

There were no clinically relevant differences in mean calcitonin levels during the trial between treatment groups. One event of increased blood calcitonin level in each treatment group was reported as well as one event of hypercalcitoninaemia in a participant in the IDegLira group. All three participants also had elevated calcitonin levels before receiving the trial drug (at screening and/or randomization) and no participants withdrew because of increased calcitonin levels.

There were no statistically significant differences in diastolic or systolic blood pressure between treatment groups. Heart rate was statistically significantly higher after 26 weeks of treatment for participants in the IDegLira group compared with the placebo group, with an ETD of 3.8 beats/min (95% CI 2.3; 5.4;  $P < 0.001$ ).

Five cardiovascular events were adjudicated (all in the IDegLira group) and four were confirmed: two were major adverse cardiovascular events, namely a myocardial infarction and a stroke. Of the 10 neoplasm events sent for adjudication, three were confirmed (one event in the IDegLira group, two events in one participant in the placebo group). One death in the IDegLira group occurred on day 116 of the trial from metastatic malignant pleural mesothelioma, which became symptomatic on day 21. The event was considered unlikely to be related to trial product; the participant had been exposed to asbestos most of his working life. One event of pancreatitis sent for adjudication was not confirmed by the external independent event adjudication committee. No thyroid-related adverse events occurred in either group.

## Discussion

This 26-week, double-blind, placebo-controlled trial investigated the safety and efficacy of IDegLira as add-on therapy in insulin-naïve adults with Type 2 diabetes inadequately controlled on sulphonylureas  $\pm$  metformin. IDegLira was

**Table 3** Treatment-emergent adverse events\*

Randomization	IDegLira (n=288)				Placebo (n=146)			
	N	%	Number of events	Events per 100 PYE	N	%	Number of events	Events per 100 PYE
Infections and infestation								
Nasopharyngitis	25	8.7	29	21.8	12	8.2	15	24.1
Influenza	8	2.8	8	6.0	8	5.5	9	14.5
Investigations								
Lipase increased	28	9.7	30	22.6	6	4.1	8	12.9
Metabolism and nutrition disorders								
Dyslipidaemia	19	6.6	19	14.3	6	4.1	7	11.3
Nervous system disorders								
Headache	15	5.2	18	13.6	8	5.5	11	17.7

PYE, patient-years of exposure.

\*Adverse events that occurred on or after the first day of exposure to treatment and no later than 7 days after the last day of treatment reported by at least 5% of participants in any one treatment group. Data are from safety analysis set.

N, number of participants with  $\geq 1$  event; %, percentage of participants.

statistically superior to placebo with regard to HbA<sub>1c</sub> reduction from baseline to week 26. Consistent with previous IDegLira trials, a high proportion of IDegLira-treated participants achieved glycaemic targets [15,16]. No between-group difference in improvement of mean postprandial increments across meals was seen in this trial in a population already being treated with an insulin secretagogue.

Sulphonylurea therapy is associated with an increased risk of hypoglycaemia and weight gain, especially when combined with insulin therapy. By the end of the trial, mean body weight for the two treatment groups had nearly converged as a result of a mean increase of 0.5 kg for the IDegLira group and a decrease of 1.0 kg with placebo. The observed rate of 3.52 events per PYE for confirmed hypoglycaemia in the IDegLira group in this trial was higher than that observed in the IDegLira group in previous DUAL phase III trials in which participants were not receiving sulphonylureas as part of the background oral antidiabetic drug therapy [15,16]. Nevertheless, the rate is in the same order of magnitude as the rates observed with concomitant administration of basal insulin and sulphonylureas [20–22]. Importantly, this comparable risk of hypoglycaemia with IDegLira was achieved at a much lower end-of-trial HbA<sub>1c</sub> compared with most previous trials of insulin initiation in Type 2 diabetes, including those combining basal insulin with sulphonylureas [20–22]. There was no significant difference in the rate of nocturnal confirmed hypoglycaemia between treatment groups.

IDegLira was well-tolerated when added to treatment with sulphonylureas ± metformin. The overall rate of adverse events was similar for the two treatment groups and similar to the rates observed in the previous IDegLira phase III trials. The higher rate of serious adverse events with IDegLira vs placebo (20.3 vs 8.0 events per 100 PYE) was largely driven by two participants experiencing seven and four serious adverse events, all of which were considered unlikely to be related to the trial product by the investigator (Table S9). The types of adverse events reported for IDegLira were consistent with the individual components and previous phase III trials involving IDegLira. There were no apparent between-treatment differences in gastrointestinal tolerability in this double-blind trial. The lack of an initial excess in gastrointestinal side effects despite the use of a GLP-1 receptor agonist probably reflects the slower and more gradual titration of liraglutide as a component of IDegLira treatment.

In summary, IDegLira can be used in people inadequately controlled with sulphonylureas ± metformin to improve glycaemic control, with a safety profile in line with previous DUAL trials. Clinicians must remain mindful of the increased risk of hypoglycaemia when insulin therapy is initiated in people already receiving sulphonylureas. When IDegLira is added to sulphonylurea therapy, a reduction in the dose of sulphonylureas should be considered, as also stated in the IDegLira prescribing information [23]. No new types or patterns of adverse events were observed. The efficacy of IDegLira was consistent with that observed in previous trials.

### Funding sources

This trial was sponsored by Novo Nordisk. The funder was responsible for trial design, product supply, monitoring, data collection, surveillance of insulin titration, safety surveillance, statistical analysis, and data interpretation, and review of the report for medical accuracy. The authors had full access to all the data in the trial and had final responsibility for the decision to submit for publication. The full trial protocol can be accessed from [clinicaltrials.gov](http://clinicaltrials.gov) NCT01618162.

### Competing interests

H.W.R. has served on advisory panels for Amylin Pharmaceuticals, Inc., AstraZeneca Pharmaceuticals LP, Bidel, Inc., Bayer Health Care, LLC, Merck, Novo Nordisk A/S, Roche Pharmaceuticals and Sanofi; as a consultant for Bidel, Inc., Merck, Roche Pharmaceuticals, and Takeda Pharmaceuticals U.S.A., Inc, Merck, Sanofi; and has received research support from AstraZeneca Pharmaceuticals LP, Bidel, Inc., Boehringer Ingelheim Pharmaceuticals, Inc., Hamni, Janssen Pharmaceuticals, Eli Lilly and Co., Merck, Novartis Pharmaceuticals Corp., Novo Nordisk A/S, Roche Pharmaceuticals and Sanofi; and has served as a speaker for AstraZeneca Pharmaceuticals LP, BMS, Boehringer Ingelheim Pharmaceuticals, Inc., Janssen, Eli Lilly and Co., Merck, Novo Nordisk A/S, Sanofi and Takeda Pharmaceuticals USA, Inc. B.W.B. has served on advisory panels and as a consultant for Novo Nordisk A/S, Janssen and Co., and Sanofi; has received research support from Novo Nordisk A/S, Eli Lilly and Co., Sanofi, Merck and Johnson & Johnson, and has served as a speaker for Novo Nordisk A/S, Eli Lilly and Co., Sanofi, Merck, GSK and AstraZeneca. H.J. and L.L. are employees of Novo Nordisk. J.T. is a consultant for Novo Nordisk and Sanofi and has received honoraria (speaking) from Novo Nordisk, Sanofi, GlaxoSmithKline, Janssen, Bristol-Myers Squibb, and AbbVie. 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, AstraZeneca Pharmaceuticals LP, Janssen, Eli Lilly and Co., Boehringer Ingelheim Pharmaceuticals, Inc and Novo Nordisk. No other potential conflicts of interest are reported.

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### Author Contributions

All authors (H.W.R., B.W.B., S.B.H., L.R., L.L., H.J. and J.T.) confirm that they meet the International Committee of Medical Journal Editors (ICJME) uniform requirements for authorship and that they have contributed to: conduct/data collection, 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 in the online version of this article:

**Table S1.** Number of randomized participants by country.

**Table S2.** Inclusion and exclusion criteria.

**Table S3.** Titration algorithm.

**Table S4.** Models of glucose meters used (all Abbott Diabetes Care).

**Table S5.** Sensitivity analyses of the primary endpoint.

**Table S6.** Daily sulphonylurea dose at screening.

**Table S7.** Adverse events related to trial product.

**Table S8.** Rates of nausea, vomiting and diarrhoea.

**Table S9.** Treatment emergent serious adverse events by systems organ class.

**Figure S1.** Percentage of participants reporting nausea by week.