Superior HbA1c control with the fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with ≤50 units insulin degludec in Japanese subjects with type 2 diabetes in a phase 3, double-blind, randomised trial

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Abstract

Aims

To investigate the efficacy and safety of insulin degludec/liraglutide (IDegLira) compared with ≤50 U insulin degludec (degludec) in Japanese subjects with type 2 diabetes (T2D).

Materials and methods

In this 26-week, double-blind, multicentre, treat-to-target trial, Japanese subjects with T2D uncontrolled with basal or pre-mix insulin (20–50 units) were randomised (1:1) to receive IDegLira or degludec both with metformin. The maximum dose was 50 dose steps (IDegLira) or 50 units (degludec). The primary endpoint was change from baseline in HbA1c of IDegLira vs degludec after 26 weeks of treatment.

Results

In total, 210 Japanese subjects were randomised to IDegLira or degludec and completion rates were 100% and 93%, respectively. IDegLira was superior to degludec for change from baseline in HbA1c: estimated treatment difference (ETD) [95% confidence interval]: –13.98 mmol/mol [–16.41; –11.55], $p<0.0001$. Mean HbA1c changed from 70.6 by −21.3 mmol/mol with IDegLira and from 70.1 by −7.1 mmol/mol with degludec. Mean change in body weight was –0.7 kg with IDegLira vs 0.7 kg with degludec (ETD: –1.41 kg [–2.26; –0.56], $p=0.0012$). Mean daily total insulin dose was significantly lower with IDegLira (37.6 U) vs degludec (41.2 U) at Week 26. Overall rates of severe or blood glucose-confirmed hypoglycaemia and adverse events were comparable between treatments.

Conclusions

IDegLira provided superior HbA1c reductions compared with ≤50U degludec, with weight loss and similar hypoglycaemia rates and no unexpected safety or tolerability issues. These results suggest that this treatment could be an attractive intensification option for Japanese subjects with T2D uncontrolled on basal or premixed insulin.

Background

Prevalence of diabetes in the Japanese adult population is projected to increase from 7.7% in 2017 to 8.3% in 2045[1], with the majority of these cases being type 2 diabetes (T2D)[2-4]. This increase in prevalence is attributed, in part, to changes in lifestyle factors such as diet and exercise[5].

Many patients with T2D will require insulin therapy due to the progressive nature of the disease[6]. Basal or pre-mix insulin, in combination with oral agents such as metformin, are established treatments for T2D in Japan[7]; however, many patients fail to achieve adequate glycaemic control and may therefore be at higher risk of developing long-term complications[8] and this may be as a result of clinical inertia[9].

Barriers to optimal insulin initiation and titration can include the increased risk of hypoglycaemia, weight gain, and the burden placed on patients' lives by the number of injections necessary to titrate and administer complex insulin regimens[10]. To help overcome some of these barriers, combination therapy with basal insulin and a glucagon-like peptide-1 receptor agonist (GLP-1RA), administered as separate injections, has been recommended by the Japanese Diabetes Society following successful outcomes from recent global trials[7]. Basal insulin and GLP-1RAs together lower fasting plasma glucose (FPG) levels and reduce post-prandial glucose excursions while limiting the risk of hypoglycaemia[11]. These effects may be particularly important in the ageing Japanese population[12].

Insulin degludec/liraglutide (IDegLira) is a fixed-ratio combination of insulin degludec (degludec) and the GLP-1RA liraglutide, administered as a once-daily single injection[13,14]. The safety and efficacy of IDegLira has been investigated in a number of patient populations in the global DUAL clinical trial programme; including the global DUAL II study, which

confirmed the superiority of IDegLira over degludec alone in terms of glycaemic control and established the contribution of the liraglutide component in IDegLira in non-Japanese subjects [15]. These trials led to the European approval of IDegLira in 2014 and US approval in 2016.

The aim of this study was to compare the efficacy and safety of IDegLira vs degludec (≤50 units) in Japanese subjects with T2D inadequately controlled on a basal or pre-mixed insulin regimen.

Research design and methods

This was a 26-week, multicentre, randomised, parallel, two-arm, treat-to-target, double-blind trial investigating the efficacy and safety of IDegLira vs degludec both in combination with metformin (**Figure 1**). Degludec was capped to the same maximum dose (50 U) across treatment groups to allow for assessment of the contribution of the liraglutide component of IDegLira. The trial consisted of a 2-week screening period, and a 26-week treatment period. Subjects were Japanese adults with a body mass index (BMI) of ≥23 kg/m^2 and HbA1c levels of 58–97 mmol/mol (7.5–11.0%), who had been diagnosed with T2D ≥6 months prior to screening, and who had been on a stable therapy with basal or pre-mix/combination insulin (20–50 units) in combination with metformin for ≥60 days prior to screening. In addition to metformin, subjects could also be receiving one of the following oral anti-diabetic drugs (OADs): sulphonylureas (SU), glinides, α-glucosidase inhibitors (α-GI), sodium-glucose cotransporter-2 inhibitors (SGLT2i) or thiazolidinediones (TZD).

The protocol was approved by independent ethics committees or institutional review boards at all participating institutions. The study was performed in accordance with the Declaration

of Helsinki and ICH Good Clinical Practice guidelines. Written consent was obtained from all subjects before enrolment.

Treatment

IDegLira and degludec were administered once daily at approximately the same time each day in a double-blind manner. The recommended starting doses were 10 dose steps of IDegLira (10 units degludec/0.36 mg liraglutide) or 10 U of degludec with the option of a higher starting dose, up to 16 dose steps of IDegLira or 16 U of degludec, at the investigator's discretion depending on the condition of the patient. Both treatments were titrated twice weekly based on the mean of three consecutive pre-breakfast self-measured blood glucose (SMBG) measurements (**Supplementary Table 1**). SMBG was assessed using a glucose meter calibrated to plasma equivalent values. The maximum dose was 50 dose steps (50 U degludec/1.8 mg liraglutide). All anti-diabetic treatments except metformin were discontinued at randomisation. Metformin was continued at the pre-trial dose; however, in case of safety concerns and at the investigator's discretion, the metformin dose could be reduced.

Stratification and randomisation

Subjects were randomised 1:1 via a central interactive voice/web system to receive either IDegLira or degludec, in combination with metformin. Subjects were stratified into four groups based on pre-trial anti-diabetic treatment regimen: metformin plus basal insulin; metformin plus basal insulin and one other OAD; metformin plus pre-mix/combination insulin; and metformin plus pre-mix/combination insulin and one other OAD.

Endpoints

The primary endpoint was change from baseline in HbA1c after 26 weeks of treatment for assessing superiority of IDegLira vs degludec. Supportive secondary efficacy endpoints included: change from baseline after 26 weeks in body weight, laboratory-measured FPG, daily insulin dose, achievement of HbA1c <53 mmol/mol (<7.0%) and ≤48 mmol/mol (≤6.5%), achievement of HbA1c targets without hypoglycaemia or weight gain, SMBG nine-point profile, systolic and diastolic blood pressure, fasting lipid profiles and patient-reported outcomes (PROs). PROs assessed were the Diabetes Therapy-Related Quality Of Life (DTR-QOL) and EuroQOL-5D-5L (EQ-5D-5L) questionnaires. Safety variables included number of treatment-emergent adverse events (TEAEs), severe or blood glucose (BG)-confirmed (<3.1 mmol/L [<56 mg/dL]) hypoglycaemic events and pulse after 26 weeks of treatment.

Statistical analysis

The primary objective was to confirm the superiority of IDegLira vs degludec regarding change from baseline in HbA1c after 26 weeks of treatment. The sample size was determined using a t-statistic with α=0.05 (two-sided test), a mean difference between treatments in change from baseline in HbA1c of –0.45% for IDegLira versus degludec for the completers, a retained effect of 0.2% for withdrawals (assumed to be 15%) and a standard deviation of 1.0%. The above assumptions are based on experience from the global DUAL phase 3 development programme for IDegLira. From these assumptions, and based on a 1:1 randomisation, the sample size was determined to be 105 subjects per treatment arm, a randomised population of at least 210 subjects. This ensured a nominal power of at least 84.5%.

Continuous efficacy endpoints including the primary endpoint were analysed separately using an analysis of covariance (ANCOVA) model including treatment, pre-trial anti diabetic treatment as fixed effects and the baseline value of the parameter as a covariate. In the primary analysis of the primary endpoint, superiority was confirmed if the 95% CI for the treatment difference was entirely below 0.0%. Insulin dose was analysed using an ANCOVA model including the same fixed effects/covariate and baseline HbA1c as an additional covariate. Last observation carried forward (LOCF) was used to impute missing values for endpoints after 26 weeks of treatment. Responder endpoints were analysed separately using a logistic regression model with treatment, pre-trial anti-diabetic treatment as fixed effects and the associated baseline values (HbA1c, and body weight [if relevant]) as covariate(s). Number of treatment-emergent hypoglycaemic episodes was analysed using a negative binominal regression model with a log-link function, with treatment and pre-trial anti-diabetic treatment as fixed effects, and the logarithm of the treatment-emergent time period (on or after the first day of treatment and no later than 7 days after the last day of treatment) as offset. A linear mixed-effect model was fitted to the nine-point SMBG profile data. The model included treatment, pre-trial anti-diabetic treatment, time, and treatment-time and pre-trial anti-diabetic treatment-time interactions as fixed factors and subject as random effect. For the fasting lipid profile, the endpoint and baseline covariates were log-transformed before the analysis, and the estimated treatment difference on a logarithmic scale was back-transformed and shown as the estimated treatment ratio. All statistical analyses of efficacy and safety endpoints were carried out using the full analysis set (FAS), defined as all subjects randomised to IDegLira or degludec. The robustness of the conclusions from the primary endpoint was assessed in sensitivity analyses using a mixed

model for repeated measurements (MMRM) and a pattern mixture model approach mimicking an intention-to-treat scenario.

Results

Subjects

Of 267 subjects screened, 210 were randomised (105 to each treatment group). No subjects in the IDegLira group withdrew from treatment compared with seven subjects (6.7%) in the degludec group. Subject disposition and reasons for withdrawal are displayed in **Supplementary Figure 1.** Baseline characteristics were similar between treatment groups and representative of a population with T2D inadequately controlled on their current treatment; treatment regimens at screening were also comparable (**Table 1** and **Supplementary Table 2**).

Primary endpoint

The primary endpoint was change from baseline in HbA1c after 26 weeks of treatment. After 26 weeks, mean HbA1c changed from 70.6 mmol/mol (8.61%) at baseline by −21.3 mmol/mol (−1.95%) with IDegLira, and from 70.1 mmol/mol (8.56%) by −7.1 mmol/mol (−0.65%) with degludec. The estimated treatment difference (ETD) was –13.98 mmol/mol [–16.41; –11.55]$_{95\%\ CI}$, (–1.28 %-points [–1.50; –1.06]$_{95\%\ CI}$), p<0.0001), confirming superiority of IDegLira vs degludec (**Figure 2A**). The conclusion from the primary analysis was supported by the sensitivity analyses.

Secondary endpoints

Body weight

From baseline to end of trial, mean body weight decreased by –0.7 kg (from 73.9 kg to 73.2 kg) with IDegLira and increased by 0.7 kg (from 75.5 kg to 76.3 kg) with degludec, representing an ETD of –1.41 kg [–2.26; –0.56]$_{95\%\ CI}$, *p*=0.0012 (**Figure 2B**).

Fasting plasma glucose

The mean change from baseline in FPG after 26 weeks was –2.8 mmol/L (–50.6 mg/dL) in the IDegLira group and –2.3 mmol/L (–41.3 mg/dL) in the degludec group (ETD after 26 weeks, –0.25 mmol/L [–0.81; 0.30]$_{95\%CI}$; –4.59 mg/dL [–14.62; 5.44]$_{95\%CI}$, *p*=0.3678, **Figure 2C**).

Insulin dose

After 26 weeks, the mean daily total insulin dose was significantly lower with IDegLira than with degludec (37.6 units vs. 41.2 units, respectively) with an ETD of –3.08 units [–6.08; –0.08]$_{95\%CI}$, *p*=0.0444 (**Figure 2D**). At end of trial, 34 (32.4%) subjects in the IDegLira group were on the maximum dose of 50 dose steps and 49 (46.7%) of subjects in the degludec group were on the maximum dose of 50 U.

HbA1c responders

The odds of achieving HbA1c targets and composite endpoints at end-of-trial were significantly higher for subjects who received IDegLira compared with degludec, (*p*<0.0001 in all cases; **Figure 3**). Of the subjects receiving maximum dose of IDegLira/degludec, 50%/18.4% achieved HbA1c <53 mmol/mol (<7%), respectively.

Nine-point SMBG profile

With the exception of at pre-breakfast, SMBG values were significantly lower with IDegLira compared with degludec (*p*-values ranged from <0.0001 to 0.024). After 26 weeks, mean

nine-point SMBG decreased by 2.9 mmol/L (52.3 mg/dL) to 8.6 mmol/L (155.0 mg/dL) with IDegLira compared with –1.1 mmol/L (20.1 mg/dL) to 10.1 mmol/L (182.0 mg/dL) with degludec. The ETD was –1.61 mmol/L $[–2.18;–1.05]_{95\%CI}$, –29.04 mg/dL $[–39.23; –18.85]_{95\%CI}$ (p<0.0001; **Supplementary Figure 2**). After 26 weeks, the mean prandial increment across all meals was smaller with IDegLira than with degludec (3.8 and 4.8 mmol/L [69.1 and 86.9 mg/dL], respectively) with an ETD of –1.08 mmol/L [–1.65;–0.50], –19.39 mg/dL $[–29.77; –9.02]_{95\%CI}$ (p=0.0003). Mean prandial glucose increment at baseline and Week 26 and statistical analyses of change from baseline in prandial glucose increments are presented in **Supplementary Table 3**.

Blood pressure

Change in systolic and diastolic blood pressure was similar for IDegLira and degludec with ETDs of –0.57 mmHg $[–4.17; 3.04]_{95\% CI}$, p=0.7575 and 0.89 mmHg $[–1.37; 3.14]_{95\% CI}$, p=0.4381 respectively (**Supplementary Table 4)**.

Fasting lipid profiles

After 26 weeks, a statistically significant treatment difference was seen in total cholesterol (favouring IDegLira), low density lipoprotein (favouring IDegLira) and high density lipoprotein (favouring degludec), while all other lipid endpoints were not statistically significant between treatment arms (**Supplementary Table 5**).

Patient reported outcomes

The change from baseline in total DTR-QOL score after 26 weeks was significantly in favour of IDegLira compared with degludec (ETD, 7.39 $[3.82; 10.97]_{95\%CI}$, p<0.0001; **Supplementary Table 6**).

Change from baseline in three of the four DTR-QOL domain scores were significantly in favour of IDegLira compared with degludec, with the largest ETDs between groups being for 'anxiety and dissatisfaction with treatment' and 'satisfaction with treatment' domains with ETDs of 11.65 $[6.92; 16.38]_{95\%CI}$ and 14.82 $[9.59; 20.05]_{95\%CI}$, respectively (both $p<0.0001$). No significant difference was seen between treatment for the hypoglycaemia domain (ETD, 0.84 $[-5.09; 6.77]_{95\%CI}$, $p=0.7807$). Change from baseline in EQ-5D-5L VAS and EQ-5D-5L index scores were also significantly in favour of IDegLira vs degludec. The ETDs were 4.67 ($[0.91; 8.43]_{95\%CI}$, $p=0.0151$) and 0.03 ($[0.01; 0.05]_{95\%CI}$, $p=0.0136$), respectively.

Safety

Adverse events

A summary of adverse events (AE) is displayed in **Table 2.** The percentage of subjects experiencing at least one AE were similar in each treatment group (78.1% with IDegLira and 76.2% with degludec) with the overall rate of events, per 100 patient years of exposure (PYE), being 515.9 with IDegLira compared with 401.8 with degludec. There were more subjects experiencing constipation, nausea (**Supplementary Figure 3**), diarrhoea and vomiting (AEs within the System Organ Class [SOC] gastrointestinal disorders) and decreased appetite (AE within the SOC metabolism and nutrition) with IDegLira compared with degludec. The most frequently reported AEs in both treatment groups were viral upper respiratory tract infection and diabetic retinopathy. The majority of AEs, in both groups, were considered by the investigator to be mild, non-serious and unlikely to be related to the trial product. The percentage of subjects with gastrointestinal AEs and AEs relating to metabolism and nutrition were higher with IDegLira (42.9% and 14.3%, respectively) compared with degludec (22.9% and 2.9%, respectively). Elevated lipase levels were

reported in two subjects, both in the IDegLira arm. These events were non-serious, mild or moderate in severity, and assessed as possibly related to trial product by the investigator. There were no AEs of increased amylase or calcitonin levels (≥20 ng/L) reported. In the degludec treatment group there was one event of pancreatic carcinoma, which led to permanent discontinuation of trial product after 2 weeks of treatment; this event was considered by the investigator to be unrelated to degludec. Eight (7.6%) subjects experienced an AE, which resulted in a dose reduction of IDegLira (at the investigator's discretion) whereas there were no reductions in degludec dose due to AEs.

Serious adverse events

Three subjects (2.9%) reported a total of four serious adverse events (SAEs) with IDegLira compared with four subjects (3.8%) reporting a total of six SAEs with degludec. In the IDegLira group, one SAE (acute myocardial infarction) was confirmed by the Event Adjudication Committee (EAC) to be a major adverse cardiovascular event; however, this did not lead to any changes in dosing. The EAC also confirmed two neoplasms (colorectal) in the IDegLira group, which were non-serious, of moderate severity and unlikely to be related to trial product. All four SAEs reported in the IDegLira group were considered to be unlikely related to treatment. In the degludec group, there was one EAC-confirmed neoplasm (pancreatic carcinoma), which was considered serious, of mild severity and unlikely related to trial product. Three of the SAEs reported in the degludec group were considered possibly related to treatment, these included two events of loss of consciousness (both related to excessive alcohol consumption) in the same subject and one event of acute cholecystitis. There were no deaths and no events of pancreatitis reported in this trial.

Hypoglycaemia

The cumulative events of severe or BG-confirmed symptomatic hypoglycaemia are displayed in **Supplementary Figure 4**. The percentage of subjects who experienced severe or BG-confirmed hypoglycaemic episodes was similar between groups (28.6% [IDegLira] vs 30.5% [degludec]; corresponding rates were 228.45 and 208.55 episodes per 100 PYE, respectively). The percentage of subjects who experienced severe or BG-confirmed symptomatic hypoglycaemic episodes was 14.3% in the IDegLira group and 17.1% in the degludec group. The corresponding rates were 95.80 and 82.27 episodes per 100 PYE, respectively. There was no statistically significant difference in the rate of severe or BG-confirmed hypoglycaemic episodes or severe or BG-confirmed symptomatic hypoglycaemic episodes between treatment groups (estimated rate ratios 1.16 $[0.57; 2.34]_{95\%CI}$, p=0.6853 and 1.05 $[0.40; 2.77]_{95\%CI}$, p=0.9184, respectively).

Pulse

After 26 weeks, change in pulse was significantly greater for IDegLira versus degludec (6.1 vs –0.2 beats/min, ETD: 7.73 beats/min $[5.45; 10.01]_{95\%\ CI}$, p<0.0001.

Discussion

The relative contribution of the liraglutide component of IDegLira was assessed whilst comparing the efficacy and safety of IDegLira vs degludec (≤50 units) in Japanese patients with T2D uncontrolled on basal insulin or pre-mix/combination insulin plus metformin (with or without one additional OAD). In this trial, IDegLira proved superior to degludec in terms of change in HbA1c levels, consistent with results from the global DUAL II trial[15]. Despite this, the rates of severe or BG-confirmed hypoglycaemia were similar between groups. The difference in HbA1c levels observed with IDegLira was achieved at a significantly lower

insulin dose than with degludec supporting a clinically significant contribution of the liraglutide component to overall glycaemic control.

Treatment effect on body weight was consistent with previous findings[15-19] (a review of which may be found in Wysham *et al.* 2018 and Aroda *et al.* 2018[20,21]), and demonstrates that the benefits of IDegLira extend beyond glycaemic control. The initial weight loss observed in both treatment groups may be due to decrease in insulin dose from pre-trial doses of approximately 28 U to starting doses of 10 dose steps/U (or up to 16 dose steps/U in some cases)[22]. The additional weight loss seen in the IDegLira group is attributed to the weight-lowering effect of liraglutide, which has been described in previous trials[23], whereas mean weight gain was observed with degludec from Week 4 as dose was titrated to achieve glycaemic control. A lower magnitude of weight loss was seen in DUAL II Japan compared with trials in the DUAL global trials; for instance, in the global DUAL II trial a mean weight reduction of 2.7 kg was observed with IDegLira (compared with no weight change with degludec), while DUAL II Japan saw a weight reduction of 0.7 kg with IDegLira. This may be attributable to the lower mean baseline BMI of the Japanese study population (27.3 kg/m^2 versus 33.6 kg/m^2 in the IDegLira arm of DUAL II Japan and global DUAL II, respectively[15]).

A higher percentage of subjects achieved HbA1c targets <53 mmol/mol (<7.0%) or ≤48 mmol/mol (≤6.5%) and the triple composite endpoints of achieving HbA1c targets without weight gain and without hypoglycaemia with IDegLira than with degludec alone after 26 weeks. This is in alignment with findings from the global DUAL II trial, in which a higher percentage of subjects reached HbA1c <53 mmol/mol (<7.0%) with IDegLira than with degludec alone[15]. The mean prandial increment across all meals was also smaller with IDegLira vs. degludec, supporting the notion that GLP1-RA helps reduce post-prandial glucose excursions. Altogether, these results demonstrate that the liraglutide component of

IDegLira (maximum dose: 50 dose steps IDegLira, comprising 1.8 mg of liraglutide) provides additional glycaemic control with the benefit of weight loss and no increase in the rates of hypoglycaemia in patients uncontrolled with basal insulin or pre-mix/combination insulin, compared with degludec (maximum dose: 50 U) alone.

IDegLira significantly improved quality of life compared with degludec as demonstrated via the DTR-QOL scores, with the biggest differences being observed in the domains relating to treatment satisfaction. There was no significant difference in the hypoglycaemia domain, which is fully compatible with the similar rates of hypoglycaemia observed in this trial. PROs were not investigated in the global DUAL II study; however, these results are aligned with those of the DUAL V trial, which also compared the safety and efficacy of IDegLira with that of a basal insulin, namely continued titration of insulin glargine 100 units/mL (IGlar U100) with no maximum dose[17]. Greater improvements in treatment burden and diabetes management were observed with IDegLira, indicating higher treatment satisfaction[17].

As per the protocol, the recommended starting dose was 10 dose steps/U of IDegLira/degludec, with the option of choosing a higher dose of up to 16 dose steps/U, at the investigator's discretion depending on the condition of the patient e.g. risk of hyperglycaemia or hypoglycaemia. Pre-trial insulin products could be administered in up to 50 units/day; therefore, a potential concern might be that this considerable decrease in dose could cause uncontrolled glycaemia. However, in the IDegLira group, FPG levels started to decrease from baseline after the first week of treatment, confirming the safety of switching to IDegLira from a higher dose of pre-trial insulin. Furthermore, despite some subjects receiving a starting dose of above 10 dose steps, this did not lead to a high rate of gastrointestinal AEs and no subjects in the IDegLira group withdrew. This is consistent with other clinical results, which reported no loss of glycaemic control and no safety concerns

when switching to a starting dose of 16 U of IDegLira from any pre-trial insulin dose between 20–50 units[17,24,25].

Overall, there were no unexpected safety or tolerability issues identified with IDegLira. The AE profile of IDegLira was consistent with that of liraglutide or degludec alone. This includes the higher incidence of gastrointestinal AEs such as diarrhoea, vomiting and nausea that were observed in the IDegLira group, which is expected from the safety profile of liraglutide. The majority of the gastrointestinal AEs leading to dose reduction (4 of 7) occurred in the early period of the study (within 10 days of treatment randomisation).

An increase in resting pulse was also observed with IDegLira, which is consistent with previous trials with IDegLira[18]. The clinical significance of this elevation is unknown but appears to be a class effect of long-acting GLP-1 RAs[26]. Of note, cardiovascular benefits over placebo have been reported for GLP-1 RAs, including liraglutide [27,28].

As with all randomised clinical trials, the findings of this trial may not be applicable to clinical practice in patients who do not fit the specified inclusion and exclusion criteria. It is unclear if patients switching from >50 U of basal or pre-mix insulin to IDegLira would experience the same outcomes. In addition, it was necessary to cap the maximum dose of degludec to 50 U, to assess the contribution of the liraglutide component. Consequently, we cannot make firm conclusions on the glucose-lowering or other effects of degludec as a sub-group of subjects in this trial may have needed more than 50 U of insulin. However, in a previous trial comparing IDegLira to liraglutide and degludec, IDegLira had superior efficacy over degludec despite there being no maximum dose[29].

Results from this trial confirm the safety and superior control over HbA1c of IDegLira vs degludec in Japanese patients with T2D treated with basal or pre-mix insulin plus metformin

(and one other OAD if required). In conclusion, IDegLira resulted in superior HbA1c reductions compared with ≤50U degludec, with weight loss and similar hypoglycaemia rates and no unexpected safety or tolerability issues. Additionally, the post-prandial increases were better controlled with IDegLira compared with degludec. These results suggest that this treatment could be an attractive intensification option for Japanese subjects with T2D uncontrolled on basal or premixed insulin.

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Author contributions

All authors 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/critically revising the article and sharing in the final responsibility for the content of the manuscript and the decision to submit it for publication. HW was signatory investigator of this clinical trial, 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.

Data sharing statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Author disclosure information

HW has acted as an advisory board member for Novo Nordisk and as a speaker for Astellas Pharma, Sanofi, Mitsubishi Tanabe Pharma, Novo Nordisk, Kowa Pharmaceutical, AstraZeneca, Takeda Pharmaceutical, Novartis, Nippon Boehringer Ingelheim, Merck Sharp & Dohme, Sumitomo Dainippon Pharma, Eli Lilly Japan, Sanwa Kagaku Kenkyusho, Ono Pharmaceutical, Kissei Pharmaceutical, and FUJIFILM Pharma and receiving grants from Astellas Pharma, Sanofi, Mitsubishi Tanabe Pharma, Novo Nordisk Pharma, AstraZeneca, Takeda Pharmaceutical, Novartis Pharma, Nippon Boehringer Ingelheim, Merck Sharp & Dohme, Sumitomo Dainippon Pharma, Eli Lilly Japan, Ono Pharmaceutical, Kyowa Hakko Kirin, Daiichi Sankyo, Terumo, Pfizer Japan, Mochida Pharmaceutical, Taisho Toyama Pharmaceutical, Johnson & Johnson, and Kowa.

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References

1. Federation ID. IDF Atlas, 8th Edition: Japan country report. http://reports.instantatlas.com/report/view/846e76122b5f476fa6ef09471965aedd/JPN. Accessed October 2018.
2. Morimoto A, Nishimura R, Tamija N. Trends in the epidemiology of patients with diabetes in Japan. *Japan Med Assoc J* 2010;53:36–40.
3. Kawaski E MN, Eguchi K. Type 1 diabetes in Japan. *Diabetologia* 2006;49:828–836.
4. Forouhi NG, Wareham NJ. Epidemiology of diabetes. *Medicine (Abingdon)* 2014;42:698-702.
5. Chan JC, Malik V, Jia W, et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA* 2009;301:2129-2140.
6. Meece J. Basal insulin intensification in patients with type 2 diabetes: A review. *Diabetes Ther* 2018;9:877-890.
7. Society JD. Treatment guide for diabetes. 2016. http://www.fa.kyorin.co.jp/jds/uploads/Treatment_Guide_for_Diabetes_2016-2017.pdf.
8. Yokoyama H, Oishi M, Takamura H, et al. Large-scale survey of rates of achieving targets for blood glucose, blood pressure, and lipids and prevalence of complications in type 2 diabetes (JDDM 40). *BMJ Open Diabetes Res Care* 2016;4:e000294.
9. Satoh J, Andersen M, Bekker Hansen B, et al. Clinical inertia in basal insulin-treated patients with type 2 diabetes - Results from a retrospective database study in Japan (JDDM 43). *PLoS One* 2018;13:e0198160.
10. Russell-Jones D, Pouwer F, Khunti K. Identification of barriers to insulin therapy and approaches to overcoming them. *Diabetes Obes Metab* 2018;20:488-496.
11. Holst JJ, Vilsboll T. Combining GLP-1 receptor agonists with insulin: therapeutic rationales and clinical findings. *Diabetes Obes Metab* 2013;15:3–14.
12. Abdelhafiz AH, Rodriguez-Manas L, Morley JE, Sinclair AJ. Hypoglycemia in older people - a less well recognized risk factor for frailty. *Aging Dis* 2015;6:156-167.
13. Novo Nordisk. Xultophy® summary of product characteristics. 2018. https://www.medicines.org.uk/emc/product/3469. Accessed July 2018.
14. Novo Nordisk. Xultophy® 100/3.6 Prescribing Information: https://www.novo-pi.com/xultophy10036.pdf [Last accessed: March 2019). 2019. https://www.novo-pi.com/xultophy10036.pdf. Accessed March 2019.
15. Buse JB, Vilsboll T, Thurman J, et al. Contribution of liraglutide in the fixed-ratio combination of insulin degludec and liraglutide (IDegLira). *Diabetes Care* 2014;37:2926-2933.
16. Gough SC, Bode B, Woo V, et al. Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naive patients with type 2 diabetes. *Lancet Diabetes Endocrinol* 2014;2:885–893.
17. Lingvay I, Pérez Manghi F, Garcia-Hernandez P, et al. Effect of insulin glargine up-titration vs insulin degludec/liraglutide on glycated hemoglobin levels in patients with uncontrolled type 2 diabetes: The DUAL V randomized clinical trial. *JAMA* 2016;315:898–907.
18. Billings LK, Doshi A, Gouet D, et al. Efficacy and safety of IDegLira versus basal-bolus insulin therapy in patients with type 2 diabetes uncontrolled on metformin and basal insulin: The DUAL VII randomized clinical trial. *Diabetes Care* 2018;41:1009–1016.

19. Philis-Tsimikas A, Billings L, Busch RS, et al. Superior efficacy of insulin degludec/liraglutide (IDegLira) vs. insulin glargine (IGlar U100) as add-on to sodium-glucose cotransporter-2 inhibitor (SGLT2i) ± oral antidiabetic drug (OAD) therapy in patients with type 2 diabetes (T2D)—DUAL IX trial. *Diabetes* 2018;67:127-OR.
20. Wysham CH, Campos C, Kruger D. Safety and Efficacy of Insulin Degludec/Liraglutide (IDegLira) and Insulin Glargine U100/Lixisenatide (iGlarLixi), Two Novel Co-Formulations of a Basal Insulin and a Glucagon-Like Peptide-1 Receptor Agonist, in Patients With Diabetes Not Adequately Controlled on Oral Antidiabetic Medications. *Clin Diabetes* 2018;36:149-159.
21. Aroda VR, Arulandu JR, Cannon AJ. Insulin/Glucagon-Like Peptide-1 Receptor Agonist Combination Therapy for the Treatment of Type 2 Diabetes: Are Two Agents Better Than One? *Clin Diabetes* 2018;36:138-147.
22. Balkau B, Home PD, Vincent M, Marre M, Freemantle N. Factors associated with weight gain in people with type 2 diabetes starting on insulin. *Diabetes Care* 2014;37:2108-2113.
23. Buse JB, Nauck M, Forst T, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. *Lancet* 2013;381:117–124.
24. Meneghini LF, Jaeckel E, Leiter LA, et al. Converting to insulin degludec/liraglutide (IDegLira) is efficacious regardless of pretrial insulin dose in patients with type 2 diabetes (T2D) uncontrolled on insulin glargine U100 (IGlar). *Diabetes* 2017;66 (Supp.1): A289 (Abstract 1093-P).
25. Billings LK, Klonoff DC, Tentolouris N, Grøn R, Halladin N, Jódar E. Efficacy of IDegLira vs. basal-bolus therapy in subjects with type 2 diabetes in DUAL VII by baseline characteristics. *Diabetes* 2018;67 (Supp.1): Abstract 997-P.
26. Robinson LE, Holt TA, Rees K, Randeva HS, O'Hare JP. Effects of exenatide and liraglutide on heart rate, blood pressure and body weight: systematic review and meta-analysis. 2013;3:e001986.
27. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;375:1834–1844.
28. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;375:311-322.
29. Gough SC, Bode BW, Woo VC, et al. One-year efficacy and safety of a fixed combination of insulin degludec and liraglutide in patients with type 2 diabetes: results of a 26-week extension to a 26-week main trial. *Diabetes Obes Metab* 2015;17:965–973.

Table 1: Baseline characteristics of subjects

	IDegLira	Degludec	Total
Full analysis set	105	105	210
Age (years)	56.6 (10.4)	55.5 (10.0)	56.0 (10.2)
Duration of diabetes (years)	14.33 (7.79)	13.77 (7.46)	14.05 (7.61)
Male (%)	66.7	60.0	63.3
Weight (kg)	73.9 (11.9)	75.5 (14.0)	74.7 (13.0)
BMI (kg/m^2)	27.3 (3.1)	28.1 (4.4)	27.7 (3.8)
FPG (mmol/L)	8.95 (2.61)	8.64 (2.52)	8.79 (2.56)
FPG (mg/dL)	161.31 (46.95)	155.62 (45.37)	158.47 (46.15)
HbA1c (mmol/mol)	70.57 (9.67)	70.06 (8.70)	70.32 (9.18)
HbA1c (%)	8.61 (0.88)	8.56 (0.80)	8.58 (0.84)
Metformin dose at screening (mg)	1171 (567)	1200 (566)	1186 (565)
Diabetes regimen at screening, n (%)			
Metformin and basal insulin	46 (43.8)	46 (43.8)	92 (43.8)
Metformin, basal insulin and one other OAD	20 (19.0)	21 (20.0)	41 (19.5)
Metformin and pre-mix/combination insulin	26 (24.8)	25 (23.8)	51 (24.3)
Metformin, pre-mix/combination insulin and one other OAD	13 (12.4)	13 (12.4)	26 (12.4)

Data are mean (SD) unless otherwise stated

BMI, body mass index; degludec, insulin degludec; FPG, fasting plasma glucose; IDegLira, insulin degludec/liraglutide; OAD, oral antidiabetic drug

Table 2. Adverse events during 26 weeks of treatment

Event	IDegLira (n=105)				Degludec (n=105)			
	n	%	E	R	n	%	E	R
AE	82	78.1	280	515.86	80	76.2	210	401.79
AE possibly or probably related to treatment	38	36.2	72	132.65	26	24.8	41	78.45
Most frequent AE (≥5% of subjects in either group)								
Gastrointestinal disorders								
Diarrhoea	15	14.3	20	36.85	5	4.8	6	11.48
Nausea	10	9.5	12	22.11	4	3.8	5	9.57
Constipation	9	8.6	10	18.42	4	3.8	4	7.65
Vomiting	9	8.6	11	20.27	2	1.9	2	3.83
Abdominal discomfort	8	7.6	8	14.74	5	4.8	5	9.57
Infections and infestations								
Viral upper respiratory tract infection	21	20.0	27	49.74	24	22.9	30	57.40
Eye disorders								
Diabetic retinopathy	17	16.2	18	33.16	17	16.2	18	34.44
Metabolism and nutrition disorders								
Decreased appetite	8	7.6	8	14.74	0	–	–	–
SAE	3	2.9	4	7.37	4	3.8	6	11.48
SAE possibly or probably related to treatment	0	-	-	-	2	1.9	3	5.74

Treatment emergent: Onset date on or after the first day of exposure to randomised treatment and no later than seven days after the last day of randomised treatment. Data based on safety analysis set

%, percentage of subjects with one or more events; AE, adverse event; E, Number of adverse events; n, Number of subjects with one or more events; R: Rate (number of adverse events divided by patient years of exposure [365.25 days] multiplied by 100); SAE, serious adverse events

Figure 1: Trial design

*OAD: one of the following oral antidiabetic drugs: sulphonylureas, glinides, α-glucosidase inhibitors, sodium-glucose co-transporter-2 inhibitors or thiazolidinediones. Maximum doses were 50 dose steps for IDegLira and 50 U for degludec. Metformin was continued at pre-trial doses

IDegLira, insulin degludec/liraglutide;OAD, oral antidiabetic drug; P, phone contact; V, site visit

Figure 2. Mean change from baseline in: HbA1c (A), body weight (B) fasting plasma glucose (C) and total daily insulin dose (D) over time

(A), (B) and (C): Full analysis set. (D): Safety analysis set

Missing values are imputed by last observation carried forward. Error bars are standard error of the mean.

EOT, end of trial; FPG, fasting plasma glucose; IDegLira, insulin degludec/liraglutide

Figure 3. Subjects achieving HbA1c outcomes of <53 mmol/mol (<7.0%) and ≤48 mmol/mol (≤6.5%) (A), subjects achieving composite outcomes with HbA1c <53 mmol/mol (<7.0%) and ≤48 mmol/mol (≤6.5%) without weight gain, without hypoglycaemia and without weight gain or hypoglycaemia (B). Hypoglycaemia was defined as severe according to ADA criteria or blood glucose-confirmed (<3.1 mmol/L [<56 mg/dL]) episodes.

Based on full analysis set. Logistic regression model with treatment and pre-trial antidiabetic treatment as factors and HbA1c baseline value (and weight) as covariate(s). Hypo: Severe or blood glucose-confirmed symptomatic hypoglycaemia during last 12 weeks of treatment. Missing values were imputed by last observation carried forward

ADA, American Diabetes Association; CI, confidence interval; hypo, hypoglycaemia; IDegLira, insulin degludec/liraglutide; OR, odds ratio