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

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Summary

Background A fixed-ratio combination of the basal insulin analogue insulin degludec and the glucagon-like peptide-1 (GLP-1) analogue liraglutide has been developed as a once-daily injection for the treatment of type 2 diabetes. We aimed to compare combined insulin degludec–liraglutide (IDegLira) with its components given alone in insulin-naive patients.

Methods In this phase 3, 26-week, open-label, randomised trial, adults with type 2 diabetes, HbA$_{1c}$ of 7–10% (inclusive), a BMI of 40 kg/m^2 or less, and treated with metformin with or without pioglitazone were randomly assigned (2:1:1) to daily injections of IDegLira, insulin degludec, or liraglutide (1·8 mg per day). IDegLira and insulin degludec were titrated to achieve a self-measured prebreakfast plasma glucose concentration of 4–5 mmol/L. The primary endpoint was change in HbA$_{1c}$ after 26 weeks of treatment, and the main objective was to assess the non-inferiority of IDegLira to insulin degludec (with an upper 95% CI margin of 0·3%), and the superiority of IDegLira to liraglutide (with a lower 95% CI margin of 0%). This study is registered with ClinicalTrials.gov, number NCT01336023.

Findings 1663 adults (mean age 55 years [SD 10], HbA$_{1c}$ 8·3% [0·9], and BMI 31·2 kg/m^2 [4·8]) were randomly assigned, 834 to IDegLira, 414 to insulin degludec, and 415 to liraglutide. After 26 weeks, mean HbA$_{1c}$ had decreased by 1·9% (SD 1·1) to 6·4% (1·0) with IDegLira, by 1·4% (1·0) to 6·9% (1·1) with insulin degludec, and by 1·3% (1·1) to 7·0% (1·2) with liraglutide. IDegLira was non-inferior to insulin degludec (estimated treatment difference –0·47%, 95% CI –0·58 to –0·36, p<0·0001) and superior to liraglutide (–0·64%, –0·75 to –0·53, p<0·0001). IDegLira was generally well tolerated; fewer participants in the IDegLira group than in the liraglutide group reported gastrointestinal adverse events (nausea 8·8 *vs* 19·7%), although the insulin degludec group had the fewest participants with gastrointestinal adverse events (nausea 3·6%). We noted no clinically relevant differences between treatments with respect to standard safety assessments, and the safety profile of IDegLira reflected those of its component parts. The number of confirmed hypoglycaemic events per patient year was 1·8 for IDegLira, 0·2 for liraglutide, and 2·6 for insulin degludec. Serious adverse events occurred in 19 (2%) of 825 patients in the IDegLira group, eight (2%) of 412 in the insulin degludec group, and 14 (3%) of 412 in the liraglutide group.

Interpretation IDegLira combines the clinical advantages of basal insulin and GLP-1 receptor agonist treatment, resulting in improved glycaemic control compared with its components given alone.

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Introduction

Type 2 diabetes is characterised by impaired insulin secretion, peripheral insulin resistance, and diminished secretion or action of incretin hormones, including glucagon-like peptide-1 (GLP-1), in response to a meal.[1,2] At diagnosis, pancreatic β-cell function has typically deteriorated by up to about 50%,[3] and with progressing disease most patients eventually require insulin treatment, usually in combination with other antidiabetic drugs, to achieve glycaemic targets.[1,4] For many patients who require insulin, treatment is started with basal insulin, which mainly addresses control of fasting blood glucose.[1] Insulin doses are generally titrated to the individual patient's needs. However, hypoglycaemia, fear of hypoglycaemia, and weight gain can be major barriers to the timely initiation and optimum use of insulin.[5]

GLP-1 analogues stimulate insulin secretion while suppressing glucagon release, but only when circulating glucose concentrations are raised, resulting in a reduced risk of hypoglycaemia. GLP-1 analogues improve control of both fasting and postprandial glucose and, by reducing hunger and food intake,[6,7] induce weight loss. Transient gastrointestinal side-effects, however, are common when GLP-1 analogue treatment is started. Findings from several

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See **Online** for appendix

studies have shown improved glycaemic control and low risk of hypoglycaemia and weight gain with combined treatment with a GLP-1 analogue and insulin.[8]

Insulin degludec–liraglutide (IDegLira) is a fixed-ratio combination of the basal insulin analogue insulin degludec and the GLP-1 analogue liraglutide, developed as a once-daily injection for the treatment of type 2 diabetes. Importantly, the formulation maintains the distinct pharmacological properties of both monocomponents, allowing us to test the hypothesis, based on previous clinical experience,[9,10] that combining the complementary effects of insulin degludec and liraglutide could have a more beneficial effect on glycaemic control than treatment with either drug individually. In this phase 3 trial, we aimed to compare the efficacy and safety of IDegLira with each of its components given alone in insulin-naive patients with type 2 diabetes.

Methods

Study design and participants

This phase 3, 26-week, randomised, open-label, three-arm, parallel-group trial was done at 271 sites in 19 countries (appendix p 8). Adults (aged 18 years and older) with type 2 diabetes, HbA_{1c} of 7–10% (inclusive), a BMI of 40 kg/m² or less, and who had been previously treated with metformin with or without pioglitazone for at least 90 days before screening were eligible for enrolment. Patients were insulin-naive and were excluded if they had been treated with GLP-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, or sulfonylureas within 90 days of screening. Full inclusion and exclusion criteria are listed in the appendix (pp 8–9).

The protocol was approved by independent ethics committees or institutional review boards at all participating institutions and the study was done in accordance with the Declaration of Helsinki[11] and Good Clinical Practice guidelines.[12] We obtained written informed consent from all patients before enrolment.

Randomisation and masking

Randomisation was done with an interactive voice or web system, with stratification by concomitant oral antidiabetic treatment, baseline HbA_{1c} ($\leq 8 \cdot 3\%$ and $> 8 \cdot 3\%$), and whether or not the patient was to participate in a meal test substudy (reported elsewhere[13,14]). Participants were randomly assigned (2:1:1) to once-daily injections of IDegLira, insulin degludec, or liraglutide. Doses were given once daily at any time of day at the discretion of the investigator and the participant, but at the same time each day. All injections were given with a 3 mL FlexPen injection device (Novo Nordisk, Bagsværd, Denmark). Treatment assignment was masked for a safety committee (responsible for safety surveillance), an independent external committee that adjudicated selected adverse events (appendix p 10), and personnel involved in defining the analysis sets until the database

was released for statistical analysis. Patients and all other investigators were not masked to treatment assignment.

Procedures

IDegLira (insulin degludec 100 U/mL plus liraglutide $3 \cdot 6$ mg/mL), insulin degludec (100 U/mL), and liraglutide (6 mg/mL) were all given subcutaneously. All three treatments could be given at any time of day provided the chosen time was used consistently every day. Metformin and pioglitazone were maintained at pretrial doses and dosing frequencies, unless documented safety reasons warranted a change. Liraglutide was started at $0 \cdot 6$ mg per day and was increased by $0 \cdot 6$ mg per week to a maximum of $1 \cdot 8$ mg per day. IDegLira was started at 10 dose steps (10 U insulin degludec plus $0 \cdot 36$ mg liraglutide, once daily); the starting dose of insulin degludec alone was 10 U once daily. On the basis of prebreakfast self-monitored blood glucose measurements (mean from three consecutive days), doses of IDegLira and insulin degludec were titrated individually twice per week to achieve a prebreakfast plasma glucose of 4–5 mmol/L (72–90 mg/dL) by use of an algorithm (appendix p 11). The daily dose of IDegLira could be titrated to 50 dose steps (50 U insulin degludec plus $1 \cdot 8$ mg liraglutide); no maximum dose was specified for insulin degludec alone.

Self-monitoring of blood glucose was done with a glucose meter (Optium Xceed; Abbott Diabetes Care, Alameda, CA, USA), calibrated to plasma values. Blood samples were taken for measurement of HbA_{1c} and fasting plasma glucose at a central laboratory (Quintiles, Livingston, UK); HbA_{1c} was measured by high-performance liquid chromatography and fasting plasma glucose by use of a colorimetric method.

Outcomes

The primary endpoint was change in HbA_{1c} from baseline after 26 weeks of treatment. Key secondary efficacy endpoints were achievement of end-of-trial HbA_{1c} of less than $7 \cdot 0\%$, or $6 \cdot 5\%$ or less, and changes in laboratory-measured fasting plasma glucose, bodyweight, insulin dose, and nine-point self-monitored blood glucose profiles (means were calculated as the area under the profile normalised by the measurement time; post-prandial plasma glucose increment was calculated as change in premeal concentration to 90 min post-meal). Only predefined confirmatory secondary endpoints and key secondary endpoints relevant for the understanding and interpretation of glycaemic control are reported.

Safety variables included adverse events, hypoglycaemic episodes, standard laboratory analyses, physical examination, vital signs, fundoscopy, and electro-cardiography (ECG). A central laboratory (Quintiles) did the laboratory analyses. Confirmed hypoglycaemia was defined as the occurrence of episodes requiring assistance (severe), or episodes in which plasma glucose concentration (determined from self-monitored blood

glucose) was less than 3·1 mmol/L (56 mg/dL), irrespective of symptoms. Adverse events of special interest included gastrointestinal symptoms, pancreatitis, increased concentrations of amylase or lipase, increased concentrations of calcitonin, death, neoplasms, thyroid disease, altered renal failure, severe hypoglycaemia, allergic reactions, immune complex disease, antibody formation, medication errors concerning trial products, suspected transmission of an infectious agent via a trial product, adverse events leading to treatment discontinuation, and major adverse cardiovascular events. Adverse events are reported by organ class. Calcitonin was measured at baseline and during the trial; all calcitonin concentrations of 10 ng/L (2·92 pmol/L) or higher were submitted to an independent calcitonin monitoring committee, together with relevant supplementary data. An independent adjudication committee masked to treatment assignment assessed any cases or suspected cases of benign or malignant neoplasms, thyroid disease, cardiovascular events, and pancreatitis (including increased concentrations of lipase or amylase with symptoms of pancreatitis; appendix p 10).

Statistical analyses

We calculated the necessary sample size on the basis of the main study objective of jointly confirming the non-inferiority of IDegLira to insulin degludec alone with an upper 95% CI margin of 0·3%, and the superiority of IDegLira to liraglutide alone with a lower 95% CI margin of 0% (with respect to change in HbA_{1c} at 26 weeks). The secondary objective was to confirm the superiority of IDegLira to insulin degludec alone on at least one of four confirmatory secondary endpoints: postprandial glucose control (determined from a standard meal test; reported elsewhere[13,14]), change in bodyweight from baseline, end-of-trial insulin dose, and number of confirmed hypoglycaemic episodes.

For the main objective, we assessed the non-inferiority of IDegLira to insulin degludec alone because the dose is capped for IDegLira and not for insulin degludec, implying that a higher insulin dose can be achieved in the insulin degludec group than in the IDegLira group. Therefore, a superiority hypothesis on glycaemic control compared with insulin degludec was not appropriate for the treat-to-target design. For IDegLira versus liraglutide, the two groups had, by design, the same maximum dose of liraglutide, such that one group could not benefit from continued up-titration. Therefore, a superiority hypothesis was valid in view of the addition of the insulin degludec component in IDegLira. The four confirmatory secondary endpoints were adjusted for multiplicity (Holm-Bonferroni method)[15] and, to maintain an overall type I error of 5% (two-sided), were only tested if the primary objective was met. Superiority for confirmatory secondary endpoints was regarded as confirmed if p values were below the Holm-Bonferroni-adjusted significance levels. We calculated that a sample size of 1660 participants was needed to confirm the primary and secondary objectives with 93·6% and more than 99% power, respectively (appendix p 12).

The primary efficacy analysis was done by ANCOVA with treatment, stratification factors, and country as fixed factors, and baseline value as covariate. We did this analysis on the full analysis set (defined as all randomly assigned patients) using last observation carried forward to impute missing values. We also analysed the primary outcome in the per-protocol analysis set (ie, all patients without any major protocol violations that might have affected the primary endpoint) and the completers analysis set (ie, all patients who completed assigned treatment). These analyses were used as sensitivity analyses for the investigation of non-inferiority. Safety analysis was done in the safety analysis set (all patients who received at least one dose of study drug). Three randonly assigned patients (one from each treatment group) were excluded from all analysis sets before unmasking of trial results because of a breach of Good Clinical Practice at one study site.

We analysed changes from baseline in bodyweight, laboratory-measured fasting plasma glucose, end-of-trial insulin dose, and parameters derived from nine-point self-monitored blood glucose profiles separately using a similar ANCOVA to that used for the primary endpoint. We analysed the categorical variables of attainment of HbA_{1c} of less than 7·0% or of 6·5% or less separately using a logistic regression model (with last observation carried forward for missing values), with the same fixed effects as used for the primary endpoint. We analysed the number of confirmed hypoglycaemic episodes for the full analysis set using a negative binomial regression model with treatment, stratification factors, and country as fixed factors and 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.

Summary statistics and plots are based on imputed data with the last observation carried forward. Data are reported with 95% CIs and p values for two-sided testing of the null hypothesis (no difference at α=0·05). No comparisons were prespecified or done to compare the effects of insulin degludec and liraglutide. All analyses were done with SAS version 9.3.

Role of the funding source

Results

Of 3004 patients screened, 1663 (mean age 55 years [SD 10], HbA_{1c} 8·3% [0·9], and BMI 31·2 kg/m² [4·8])

were randomly assigned to a treatment group and 1444 completed the trial (figure 1). Treatment groups were well matched with respect to baseline clinical and demographic characteristics (table 1). The median doses of metformin (2000 mg per day) and pioglitazone (30 mg per day) at baseline were similar in all three treatment groups and did not change during the trial (appendix p 10). A higher proportion of participants withdrew from the liraglutide group (18% [73/414]) than from the IDegLira (12% [98/833]) or insulin degludec (12% [48/413]) groups during the trial (appendix p 3). Most of these withdrawals were caused by gastrointestinal adverse events.

After 26 weeks, mean HbA$_{1c}$ had decreased by 1·9% (SD 1·1) to 6·4% (1·0) with IDegLira, by 1·4% (1·0) to 6·9% (1·1) with insulin degludec, and by 1·3% (1·1) to 7·0% (1·2) with liraglutide (figure 2A). IDegLira was associated with a greater reduction in HbA$_{1c}$ than insulin

and liraglutide, meeting the criteria for non-inferiority to insulin degludec (estimated treatment difference –0·47%, 95% CI –0·58 to –0·36, p<0·0001) and superiority to liraglutide (–0·64%, –0·75 to –0·53, p<0·0001). All sensitivity analyses substantiated these results (appendix p 12).

A higher proportion of patients achieved an HbA$_{1c}$ of less than 7·0% after 26 weeks with IDegLira than with insulin degludec (81% [671/833] vs 65% [269/413], odds ratio [OR] 2·38, 95% CI 1·78–3·18, p<0·0001) or liraglutide (60% [250/414], OR 3·26, 2·45–4·33, p<0·0001; appendix p 4). Similarly, the proportion of patients who attained an HbA$_{1c}$ of 6·5% or less was higher for IDegLira than for insulin degludec (70% [581/833] vs 47% [196/413], OR 2·82, 2·17–3·67, p<0·0001) or liraglutide (41% [170/414], OR 3·98, 3·05–5·18, p<0·0001; appendix p 4). The proportion of patients who achieved HbA$_{1c}$ targets of less 7·0% and of 6·5% or less without weight gain, with
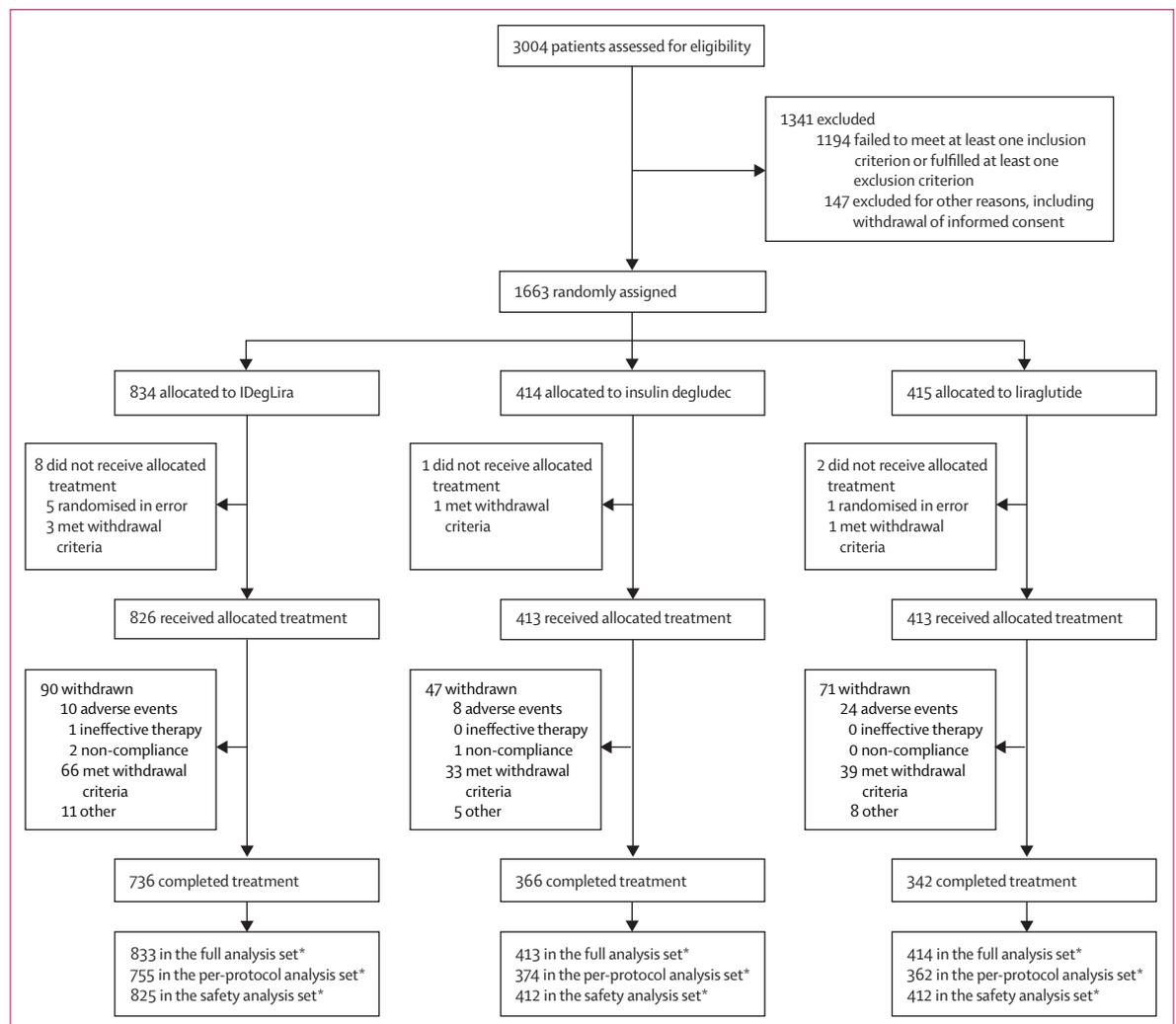

***Figure 1:* Trial profile**
IDegLira=insulin degludec–liraglutide. *Three patients (one from each treatment group) were excluded from all analysis sets before unmasking of trial results because of a breach of Good Clinical Practice at one study site.

or without confirmed hypoglycaemia, were significantly higher with IDegLira than with insulin degludec (table 2). More patients on liraglutide alone than on IDegLira achieved the HbA$_{1c}$ target of less than 7·0% without weight gain and with or without hypoglycaemia.

Mean laboratory-measured fasting plasma glucose concentrations decreased from baseline by 3·6 mmol/L (both IDegLira and insulin degludec) and 1·8 mmol/L (liraglutide) to end-of-trial values of 5·6 mmol/L (SD 1·8; IDegLira), 5·8 mmol/L (2·3; insulin degludec), and 7·3 mmol/L (2·5; liraglutide; figure 2B). We noted no significant difference between IDegLira and insulin degludec with respect to reduction in fasting plasma glucose from baseline (estimated treatment difference –0·17 mmol/L, 95% CI –0·41 to 0·07, p=0·16), whereas the reduction was greater for IDegLira than for liraglutide (–1·76, –2·00 to –1·53, p<0·0001; the appendix [p 13] includes plasma glucose values expressed in mg/dL).

After 26 weeks, the overall mean plasma glucose concentration of the nine-point self-monitored blood glucose profile had decreased to 7·1 mmol/L (SD 1·8) with IDegLira, 7·4 mmol/L (2·0) with insulin degludec, and 8·0 mmol/L (1·8) with liraglutide (see full profiles in appendix [p 5]). The reduction in mean plasma glucose concentrations was greater for IDegLira than for insulin degludec (3·2 vs 3·0 mmol/L; estimated treatment difference –0·30 mmol/L, 95% CI –0·50 to –0·09, p=0·0040) or liraglutide (2·1 mmol/L; –0·93 mmol/L, –1·13 to –0·73, p<0·0001). IDegLira reduced mean postprandial plasma glucose increment over all main meals more than did insulin degludec (estimated treatment difference –0·45 mmol/L, –0·63 to –0·28, p<0·0001), whereas IDegLira and liraglutide showed similar reductions (0·06 mmol/L, –0·11 to 0·23, p=0·48). Likewise, for each individual meal, we noted significantly greater reductions in postprandial plasma glucose increment (of a similar size) for IDegLira than for insulin degludec, whereas we noted no significant differences between IDegLira and liraglutide (appendix p 5).

Mean daily dose–time profiles are shown in figure 2 (C, D). At week 26, mean insulin dose was 28% lower with IDegLira than with insulin degludec (38 U [SD 13] vs 53 U [28]; estimated treatment difference –14·90 U, 95% CI –17·14 to –12·66, p<0·0001). In total, 324 (39%) of 833 patients received the maximum dose of IDegLira, of whom 239 (74%) achieved an HbA$_{1c}$ of less than 7·0%. Mean liraglutide doses were lower for the IDegLira group than for the liraglutide group throughout the trial and at week 26 were 1·4 mg (SD 0·5) and 1·8 mg (0·5), respectively.

From baseline to the end of the trial, mean bodyweight decreased by 0·5 kg (SD 3·5) with IDegLira, increased by 1·6 kg (4·0) with insulin degludec, and decreased by 3·0 kg (3·5) with liraglutide (figure 2E; estimated treatment difference for IDegLira vs insulin degludec, –2·22 kg, 95% CI –2·64 to –1·80, p<0·0001; IDegLira vs liraglutide, 2·44 kg, 2·02 to 2·86, p<0·0001).

	IDegLira (n=833)	Insulin degludec (n=413)	Liraglutide (n=414)
Female	398 (48%)	213 (52%)	206 (50%)
Ethnic origin			
White	513 (62%)	257 (62%)	258 (62%)
Black	72 (9%)	23 (6%)	28 (7%)
Asian	228 (27%)	120 (29%)	116 (28%)
Other	18 (2%)	11 (3%)	11 (3%)
Age (years)	55·1 (9·9)	54·9 (9·7)	55·0 (10·2)
Bodyweight (kg)	87·2 (19·0)	87·4 (19·2)	87·4 (18·0)
BMI (kg/m²)	31·2 (5·2)	31·2 (5·3)	31·3 (4·8)
Duration of diabetes (years)	6·6 (5·1)	7·0 (5·3)	7·2 (6·1)
HbA$_{1c}$ (%)	8·3 (0·9)	8·3 (1·0)	8·3 (0·9)
HbA$_{1c}$ (mmol/mol)*	67·0 (9·7)	67·3 (10·7)	66·8 (10·3)
Fasting plasma glucose (mmol/L)	9·2 (2·4)	9·4 (2·7)	9·0 (2·6)
Oral antidiabetic drug at screening			
Metformin	691 (83%)	343 (83%)	338 (82%)
Metformin plus pioglitazone†	142 (17%)	70 (17%)	75 (18%)

Data are n (%) or mean (SD). The median daily dose of metformin at screening was 2000 mg; the median daily dose of pioglitazone at screening was 30 mg (see appendix p 10 for more details). IDegLira=insulin degludec–liraglutide. *Calculated by use of the formula: HbA$_{1c}$ (mmol/mol)=(HbA$_{1c}$ [%] – 2·15)×10·929. †One patient in the liraglutide group was receiving metformin plus glimepiride at screening.

Table 1: Baseline characteristics

263 (32%) of 825 patients in the IDegLira group, 159 (39%) of 412 patients in the insulin degludec group, and 28 (7%) of 412 patients in the liraglutide group had confirmed hypoglycaemia (appendix p 13). Confirmed hypoglycaemia occurred more frequently in the IDegLira group than in the liraglutide group (estimated rate ratio 7·61, 95% CI 5·17–11·21, p<0·0001), but less frequently in the IDegLira group than in the insulin degludec group (0·68, 0·53–0·87, p=0·0023; figure 2F). IDegLira was associated with a lower risk of confirmed hypoglycaemia than insulin degludec for any given end-of-trial HbA$_{1c}$ concentration (post-hoc analysis; appendix p 6). Five severe hypoglycaemic episodes were reported (three episodes among 825 participants in the IDegLira group and two episodes among 412 participants in the insulin degludec group).

521 (63%) of 825 patients in the IDegLira group, 248 (60%) of 412 patients in the insulin degludec group, and 299 (73%) of 412 patients in the liraglutide group reported treatment-emergent adverse events (appendix p 14); most of these events (more than 95%) were mild or moderate in severity, and judged unlikely to be related to the study treatment. Overall, the most frequently occurring adverse events were headache, nasopharyngitis, and gastrointestinal disorders. A larger proportion of patients reported gastrointestinal adverse events with liraglutide than with IDegLira, but more patients reported gastrointestinal symptoms with IDegLira than with insulin degludec (table 3). Nausea was most prevalent in the first 10 weeks of the trial (appendix p 7). Overall, 73 (9%) of 825 participants in the IDegLira group
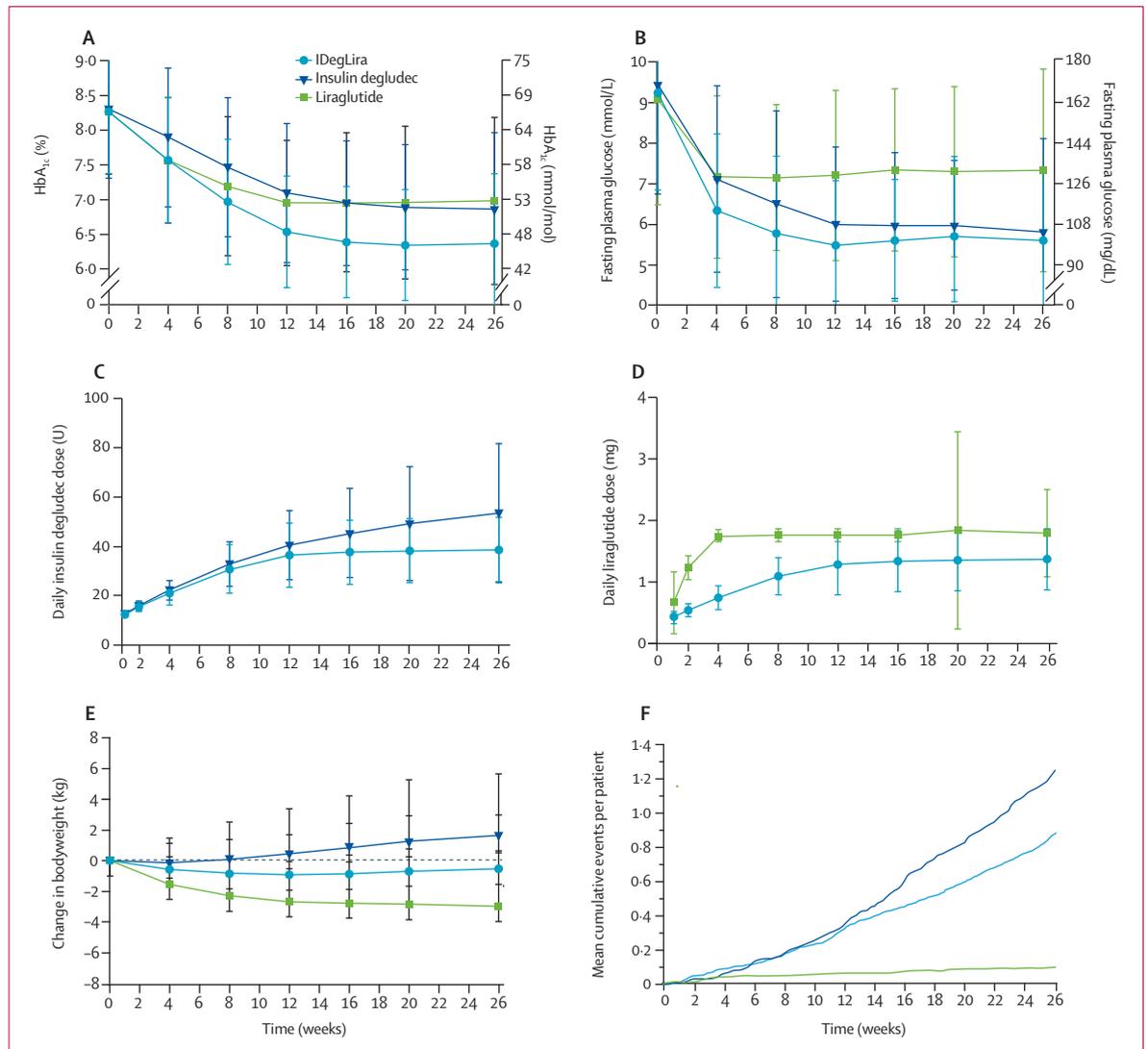
***Figure 2:* Glycaemic efficacy, doses, bodyweight, and cumulative hypoglycaemia over 26 weeks**
Mean HbA$_{1c}$ (A), fasting plasma glucose (B), insulin degludec dose (C), liraglutide dose (D), and change in bodyweight (E), plus cumulative mean number of hypoglycaemic episodes per patient (F). Error bars show SDs.

experienced nausea, compared with 81 (20%) of 412 in the liraglutide group and 15 (4%) of 412 in the insulin degludec group.

Serious adverse events occurred in 19 (2%) of 825 patients in the IDegLira group, eight (2%) of 412 in the insulin degludec group, and 14 (3%) of 412 in the liraglutide group (appendix p 14). Of 18 pancreatitis or suspected pancreatitis events across all groups (in 16 patients) assessed, one event in a patient receiving liraglutide was confirmed to be acute pancreatitis by the independent adjudication committee (and was judged by the investigator as unlikely to be related to study drug). No medullary thyroid carcinomas were reported, and no thyroid neoplasms were confirmed by the committee. Of 18 adverse cardiovascular events (in 14 patients), three

adverse events were adjudicated as major adverse cardiovascular events by the committee: a cardiovascular-related death (no autopsy done) in the IDegLira group was judged by the investigator as unlikely to be related to study drug; one case of myocardial infarction in the insulin degludec group was judged as unlikely to be related to study drug; and one case of myocardial infarction in the liraglutide group was judged as possibly related to study drug.

Mean change from baseline in pulse was greater for IDegLira than for insulin degludec (estimated treatment difference 3·2 beats per min [bpm], 95% CI 2·2 to 4·2, p<0·0001) and similar to liraglutide (−0·2 bpm, −1·2 to 0·8, p=0·72). We noted small increases from baseline to the end of the trial in mean

	IDegLira (n=833)	Insulin degludec (n=413)	Odds ratio (95% CI) for IDegLira vs insulin degludec, p value	Liraglutide (n=414)	Odds ratio (95% CI) for IDegLira vs liraglutide, p value
HbA$_{1c}$ <7·0%	671 (81%)	269 (65%)	2·38 (1·78–3·18), p<0·0001	250 (60%)	3·26 (2·45–4·33), p<0·0001
HbA$_{1c}$ <7·0%, without weight gain	385 (46%)	87 (21%)	3·49 (2·63–4·67), p<0·0001	225 (54%)	0·71 (0·56–0·91), p=0·0070
HbA$_{1c}$ <7·0%, without hypoglycaemia*	503 (60%)	169 (41%)	2·28 (1·78–2·92), p<0·0001	239 (58%)	1·13 (0·89–1·45), p=0·32
HbA$_{1c}$ <7·0%, without weight gain or hypoglycaemia*	296 (36%)	58 (14%)	3·56 (2·59–4·90), p<0·0001	215 (52%)	0·49 (0·38–0·63), p<0·0001
HbA$_{1c}$ ≤6·5%	581 (70%)	196 (47%)	2·82 (2·17–3·67), p<0·0001	170 (41%)	3·98 (3·05–5·18), p<0·0001
HbA$_{1c}$ ≤6·5%, without weight gain	349 (42%)	60 (15%)	4·71 (3·42–6·47), p<0·0001	162 (39%)	1·16 (0·90–1·49), p=0·26
HbA$_{1c}$ ≤6·5%, without hypoglycaemia*	435 (52%)	113 (27%)	3·06 (2·35–3·99), p<0·0001	164 (40%)	1·74 (1·36–2·23), p<0·0001
HbA$_{1c}$ ≤6·5%, without weight gain or hypoglycaemia*	269 (32%)	38 (9%)	5·03 (3·47–7·30), p<0·0001	156 (38%)	0·79 (0·61–1·02), p=0·066

Data are n (%), unless otherwise indicated. IDegLira=insulin degludec–liraglutide. *Without hypoglycaemia in the last 12 weeks of treatment.

Table 2: Proportions of patients reaching HbA$_{1c}$ targets

concentrations of lipase (of 11–15 U/L) and amylase (of 7–9 U/L) with IDegLira and liraglutide (appendix p 15). Most of the 178 events of increased lipase or amylase were asymptomatic and of unknown clinical relevance. However, 17 of these events (in 15 patients) were symptomatic and suspected to be related to pancreatitis and were sent for external adjudication. One of these 17 events was confirmed to be acute pancreatitis by the independent adjudication committee. We noted no clinically relevant changes in other biochemistry (or haematology) parameters in any of the treatment groups. Similarly, we noted no clinically relevant differences in physical examination, fundoscopy, or ECG findings between the treatment groups.

Discussion

In this 26-week, phase 3 trial, IDegLira produced a significantly greater improvement in glycaemic control (as measured by changes in HbA$_{1c}$) than insulin degludec or liraglutide, which was paralleled by a significantly higher proportion of patients attaining HbA$_{1c}$ targets of less than 7·0% and of 6·5% or less at end of trial. Because IDegLira and insulin degludec were titrated to similar end-of trial prebreakfast plasma glucose concentrations, the greater reduction in HbA$_{1c}$ with IDegLira seems to be attributable to the additional postprandial glycaemic control afforded by the liraglutide component of the combination product. For each main meal, reductions in postprandial plasma glucose increment with IDegLira were significantly greater than with insulin degludec, whereas the effects of IDegLira and liraglutide were similar, suggesting that the effect of liraglutide on postprandial glycaemic control was maintained when used in combination with exogenous insulin.

A similar effect of IDegLira and insulin degludec on fasting plasma glucose concentrations was accomplished as a result of the titration algorithm. The mean basal insulin dose with IDegLira was significantly lower than

	IDegLira (n=825)		Insulin degludec (n=412)		Liraglutide (n=412)	
	n (%)	Rate	n (%)	Rate	n (%)	Rate
Nausea	73 (9%)	20·9	15 (4%)	8·8	81 (20%)	54·3
Diarrhoea	66 (8%)	23·5	19 (5%)	10·3	52 (13%)	39·8
Vomiting	32 (4%)	10·1	6 (1%)	3·1	35 (8%)	23·6
Headache	87 (11%)	43·8	38 (9%)	50·7	49 (12%)	41·4
Nasopharyngitis	75 (9%)	22·4	36 (9%)	22·3	39 (9%)	27·4
Increased lipase concentration*	41 (5%)	11·3	14 (3%)	7·2	22 (5%)	12·9
Decreased appetite	20 (2%)	5·4	1 (<1%)	0·5	28 (7%)	16·1

Table shows treatment-emergent adverse events (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 the safety analysis set. Rate is the unadjusted number of events per 100 patient-years of exposure. IDegLira=insulin degludec–liraglutide. *Increased amylase concentration was reported by 15 (2%) patients in the IDegLira group, five (1%) patients in the insulin degludec group, and seven (2%) patients in the liraglutide group (see appendix p 15 for values).

Table 3: Treatment-emergent adverse events that occurred in at least 5% of patients in any treatment group

with insulin degludec, showing an effect of the liraglutide component of the combination product on fasting plasma glucose.

IDegLira was generally well tolerated; we noted no clinically relevant differences between treatments with respect to standard safety assessments, and the adverse event profile of IDegLira reflected those of insulin degludec[16,17] and liraglutide.[18] Transient gastrointestinal symptoms occurred less frequently with IDegLira than with liraglutide, particularly in the first 10 weeks of treatment. Notably, nausea occurred less frequently with IDegLira than with liraglutide alone. This finding was probably caused by the lower initial dose and the more gradual increase in liraglutide dose during IDegLira dose titration, as well as the lower mean liraglutide dose used with IDegLira treatment nearer the end of the trial.

The rate of confirmed hypoglycaemia was significantly lower with liraglutide than with IDegLira, which was

expected because GLP-1 receptor agonist treatment carries a low risk of hypoglycaemia. However, IDegLira was associated with a significantly lower rate of confirmed hypoglycaemia than was insulin degludec, probably because of the lower mean insulin dose used with IDegLira, as well as the possibility that the liraglutide component of IDegLira might have glucose-dependent beneficial effects on both α-cell (glucagon-secreting) and β-cell (insulin-secreting) function.[19–22] A small and similar number of severe hypoglycaemia episodes occurred in the IDegLira and insulin degludec groups, whereas none were recorded in the liraglutide group. Importantly, the significantly better overall glycaemic control provided by IDegLira compared with insulin degludec did not come at an increased risk of hypoglycaemia, which is often a clinical barrier for tight glycaemic control. Indeed, IDegLira had a lower risk of confirmed hypoglycaemia than insulin degludec at any given concentration of HbA_{1c}.

IDegLira treatment was not associated with weight gain, by contrast with insulin degludec. Thus, the tendency towards weight gain often associated with insulin seemed to be counterbalanced by the weight-reducing effect of the liraglutide component; the lower mean basal insulin dose used with IDegLira might also have contributed to this outcome.

In summary, IDegLira combines the clinical advantages and mitigates the principal side-effects of basal insulin (weight gain and hypoglycaemia) and GLP-1 receptor agonist treatment (gastrointestinal adverse events; panel). Further studies and feedback about patient experience are needed to determine whether these benefits of combined treatment will be compelling to health-care providers and patients, compared with the existing approach of adding basal insulin to GLP-1 receptor agonist treatment.

Panel: Research in context

Systematic review

We searched PubMed for reports of clinical research studies published in English between Dec 1, 2011, and Dec 31, 2013, using the combined search terms "insulin", "GLP-1", and "combination". The safety and effectiveness of a fixed-ratio combination of a glucagon-like peptide-1 (GLP-1) analogue and a basal insulin has not previously been compared with its individual components in a clinical trial. Results of studies in which a GLP-1 receptor agonist was added as a second injection to existing basal insulin treatment, or vice versa, suggest that this strategy improves glycaemic control while ameliorating the weight gain and risk of hypoglycaemia associated with insulin treatment.[2,8,23–25]

Interpretation

In this 26-week, phase 3 trial a dose-titratable combination of a basal insulin analogue (insulin degludec) and a GLP-1 analogue (liraglutide; IDegLira) produced a significantly greater reduction in HbA_{1c} than either of its components given alone, and enabled a greater proportion of patients to reach glycaemic targets, without weight gain and with a lower rate of hypoglycaemia than insulin degludec given alone. IDegLira also provided significantly better postprandial glucose control than insulin degludec, and was associated with fewer gastrointestinal side-effects than was liraglutide. Our findings support the rationale for basal insulin–GLP-1 analogue combination treatment and suggest that treatment with a once-daily, single-injection combination product is a suitable treatment option that can combine the benefits and mitigate the main side-effects of basal insulin and GLP-1 analogue treatments.

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