Durability of insulin degludec plus liraglutide versus insulin glargine U100 as initial injectable therapy in type 2 diabetes (DUAL VIII): a multicentre, open-label, phase 3b, randomised controlled trial

Vanita R Aroda, Guillermo González-Galvez, Randi Grøn, Natalie Halladin, Martin Haluzík, György Jermendy, Adri Kok, Petra Őrsy, Mohamed Sabbah, Giorgio Sesti, Robert Silver

Lancet Diabetes Endocrinol 2019; 7: 596–605

Published Online June 9, 2019 http://dx.doi.org/10.1016/S2213-8587(19)30184-6

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Brigham and Women's Hospital, Boston, MA, USA (V R Aroda MD); **MedStar Health Research Institute, Hyattsville, MD, USA** (V R Aroda); **Jalisco Institute of Research in Diabetes and Obesity SC, Guadalajara, Jalisco, Mexico** (G González-Galves MD); **Novo Nordisk A/S, Søborg, Denmark** (R Grøn PhD, N Halladin MD, P Őrsy MD); **Institute for Clinical and Experimental Medicine and Institute of Endocrinology, Prague, Czech Republic** (Prof M Haluzík MD); **Bajcsy-Zsilinszky Hospital, Budapest, Hungary** (G Jermendy MD); **Union and Clinton Hospitals in Alberton, Gauteng, South Africa** (A Kok MD); **Hadassah University Hospital, Jerusalem, Israel** (M Sabbah MD); **Department of Medical and Surgical Sciences, University Magna Graecia of Catanzaro, Catanzaro, Italy** (Prof G Sesti MD); **and Southern New Hampshire Diabetes and Endocrinology, Nashua, NH, USA** (R Silver MD)

Correspondence to: Dr Vanita R Aroda, Brigham and Women's Hospital, Boston, MA 2115, USA **varoda@bwh.harvard.edu**

Summary

Background Durability of glycaemic control might reduce disease burden and improve long-term outcomes. DUAL VIII investigated the durability of insulin degludec plus liraglutide (IDegLira) versus insulin glargine 100 units/mL (IGlar U100) in patients with type 2 diabetes with the use of a visit schedule that mirrored routine clinical practice.

Methods In this 104-week international, multicentre, open-label, phase 3b randomised controlled trial, insulin-naive patients aged 18 years and older, with HbA_{1c} between 7·0–11·0% (53–97 mmol/mol), BMI of 20 kg/m² or higher, on stable doses of oral antidiabetic drugs, were recruited from outpatient clinics. Patients were randomly assigned 1:1, with a simple sequential allocation randomisation schedule (block size of four), to IDegLira or IGlar U100, each treatment being an add-on to existing therapy. The internal safety committee, the independent external committee, and the personnel involved in defining the analysis sets were masked until the database was released for statistical analysis. Patients and all other investigators were not masked. In the IDegLira group, patients were given degludec 100 units/mL plus liraglutide 3·6 mg/mL in a 3 mL prefilled PDS290 pen for subcutaneous injection; in the IGlar U100 group, patients were given IGlar U100 solution, in a 3 mL prefilled Solostar pen for subcutaneous injection. Both treatments were given once daily at any time of day and it was recommended that the time of day remained the same throughout the trial. The primary endpoint was time from randomisation to need for treatment intensification (HbA_{1c} ≥7·0% [53 mmol/mol] at two consecutive visits, including week 26). Once patients met this criterion, the trial product was permanently discontinued and patients were not withdrawn from trial but rather remained on follow-up for the entire treatment and follow-up period. The primary analysis was in the intention-to-treat population. This study is registered with ClinicalTrials.gov, number NCT02501161.

Findings From Jan 8, 2016, to Oct 3, 2018, 1345 patients were screened, of which 1012 (75·2%) were eligible and randomly assigned to either IDegLira (n=506) or IGlar U100 (n=506). 484 (96%) of 506 in the IDegLira group and 481 (95%) of 506 in the IGlar U100 group completed the trial. Baseline characteristics were similar and representative of patients eligible for basal insulin intensification (overall mean diabetes duration 10 years; HbA_{1c} 8·5% [69 mmol/mol]; fasting plasma glucose 10 mmol/L). Patients in the IDegLira group had significantly longer time until intensification was needed than those in the IGlar U100 group (median >2 years *vs* about 1 year). Fewer patients in the IDegLira group needed treatment intensification over 104 weeks than those in the IGlar U100 group (189 [37%] of 506 *vs* 335 [66%] of 506). The preplanned sensitivity analyses of the primary endpoint were in agreement with the primary analysis (hazard ratio 0·45 [95% CI 0·38–0·54]) in the proportional hazards regression model and the generalised log-rank test was also in favour of IDegLira (p<0·0001). No new or unexpected safety and tolerability issues were identified and there were no treatment-related deaths.

Interpretation In patients with uncontrolled type 2 diabetes on oral antidiabetic drugs, initial injectable therapy with IDegLira resulted in fewer patients reaching the treatment intensification criterion during 104 weeks versus IGlar U100, with longer durability of the treatment effect with IDegLira.

Funding Novo Nordisk.

Introduction

Reaching and maintaining glycaemic targets (generally accepted as a HbA_{1c} of <7·0% [53 mmol/mol] for most adults)[1] reduces complications associated with diabetes.[2] The progressive nature of type 2 diabetes often necessitates treatment intensification, including addition of insulin, as the disease advances.[3] In clinical practice, patients with diabetes often do not reach their HbA_{1c} targets.[4,5] Health-care professionals and patients might be reluctant to intensify therapy as recommended in clinical

Research in context

Evidence before this study

Two 26-week clinical trials (DUAL I and IX) have shown the efficacy and safety of insulin degludec plus liraglutide (IDegLira) versus basal insulin in insulin-naive patients. Given the progressive nature of type 2 diabetes, a more durable therapy might help patients maintain glycaemic control over time and thus minimise exposure to hyperglycaemia, the need for contact with health-care professionals, and changing or adding other treatments. Few trials, such as the ADOPT and EUREXA studies, have studied treatment durability and time to recommended intensification. To date, no trials have investigated the difference in durability of initial insulin treatment options, including basal insulin plus glucagon-like peptide-1 receptor agonist (GLP-1RA) fixed ratio combination therapy versus basal insulin alone.

Added value of this study

Greater durability of treatment effect with IDegLira versus insulin glargine 100 units/mL (IGlar U100) was shown in this first trial (DUAL VIII) set out to investigate the durability of a basal insulin plus GLP-1RA combination therapy versus basal insulin. Importantly, DUAL VIII used a visit schedule designed to reflect clinical practice. Trial visits were at 3-month intervals after week 12, and broad inclusion criteria were specified (including patients with types 2 diabetes uncontrolled with oral antidiabetic drugs and HbA_{1c} 7·0–11·0% [53–97 mmol/mol]). Furthermore, in patients who did not need treatment intensification, IDegLira provided a greater treatment effect, with more patients achieving HbA_{1c} of less than 7·0% (<53 mmol/mol), HbA_{1c} of less than 7·0% (<53 mmol/mol) without weight gain, a lower estimated mean insulin dose, and lower rate of severe or blood glucose-confirmed symptomatic hypoglycaemic events per patient year of exposure versus IGlar U100. The design and primary endpoint offer translatability and applicability to the clinical setting, in which decisions on therapeutic choices are based on multiple factors, including glycaemic-lowering efficacy, and long-term outcomes, including durability.

Implications of all the available evidence

The greater durability of treatment effect with IDegLira versus IGlar U100 reported here, along with the previously reported benefits of IDegLira on glycaemic control, illustrate the effectiveness of IDegLira as an option when considering initial insulin therapy for patients with uncontrolled type 2 diabetes.

guidelines.[1,3,6] This failure to intensify treatment or establish appropriate targets is referred to as clinical inertia, which might result in prolonged exposure to hyperglycaemia. Clinical inertia can delay the initiation and intensification of insulin therapy,[7,8] which can be partly due to concerns regarding hypoglycaemia and weight gain,[7,8] often associated with insulin use.

A treatment with durable effect can be defined as one that requires fewer interventions over time compared with other treatments. Durability of pharmacotherapy is an important consideration in the treatment of type 2 diabetes; it minimises the risk of exposure to hyperglycaemia, might simplify regimens eventually needed to maintain glycaemic goals, and might provide an indication of successful treatment of the underlying complex pathophysiology of the disease. Furthermore, a durable treatment requiring fewer interventions could positively influence patients' perceptions around their diabetes management.[9]

Evidence that compares the durability of type 2 diabetes medications, particularly for injectable therapies, is scarce. The ADOPT study[10] investigated the durability of initial oral antidiabetic drug monotherapy choices; the EUREXA trial[11] investigated the durability of the glucagon-like peptide-1 receptor agonist (GLP-1RA) exenatide, twice daily, versus glimepiride; and the GRADE trial[12] is ongoing and investigating the metabolic durability of treatment choices after metformin (glimepiride, sitagliptin, liraglutide, insulin glargine 100 units/mL [IGlar U100]). Due to the chronic nature of type 2 diabetes, studies of greater length than typical treat-to-target efficacy trials lasting 26 weeks are needed to understand the efficacy of treatment choices and therapy durability.

Insulin degludec plus liraglutide (IDegLira) is a once daily, fixed ratio combination of the long-acting basal insulin degludec and the GLP-1RA liraglutide, with complementary mechanisms that could potentially target overlapping or distinct underlying pathophysiological defects of type 2 diabetes.[13–15] Degludec provides consistent and stable blood glucose concentration lowering over 24 h,[16] but common side-effects include hypoglycaemia[17] and weight gain.[18] Liraglutide acts in a glucose-dependent manner and decreases bodyweight, but can be associated with gastrointestinal side-effects.[19] The DUAL clinical trial programme investigated the efficacy and safety of IDegLira in patients as a first injectable, and in patients previously receiving either basal insulin or GLP-1RA therapy.[20–27] The DUAL trials showed that IDegLira improved glycaemic control with weight benefit and similar or lower rates of hypoglycaemic events per patient year of exposure compared with basal insulin[20,21,24,27] and a lower incidence of gastrointestinal adverse events than with GLP-1RAs alone.[20,22] However, previous DUAL trials investigated the effects of IDegLira for 26 or 32 weeks, with the DUAL I extension[28] being the longest trial of IDegLira to date, lasting 52 weeks.

DUAL VIII was a 104-week trial that compared the durability of IDegLira versus IGlar U100 in insulin-naive patients with type 2 diabetes inadequately controlled with

oral antidiabetic drugs and thus aimed to compare two treatment alternatives in patients for whom insulin therapy would be a reasonable treatment choice. DUAL VIII was designed to mirror recommended routine clinical practice and decision making, following recommendations from an expert consensus statement,[3] with only three visits before week 12 during initial titration followed by visits scheduled every 3 months for timely assessment of treatment effect and requirement for treatment intensification.

Methods

Study design

See Online for appendix

DUAL VIII was a phase 3b, open-label, two-arm parallel, randomised trial of patients with type 2 diabetes from 130 outpatient clinic sites (appendix p 1). The trial lasted 110 weeks, consisting of a 2-week screening period, a 104-week treatment period, and two follow-up safety assessments at 7 days (+3) and 30 days (+3) after the last dose of trial product (appendix p 23). Patients attended three visits during the period between randomisation and week 12 (at weeks 1, 2, and 4) for treatment initiation and titration. The visit schedule was the same for patients regardless of whether they were in glycaemic control. After week 12, visits were scheduled once every 3 months for patients not requiring treatment intensification, mirroring current standards of clinical practice. Patients who discontinued the trial product prematurely for any reason (including the need for treatment intensification) were called in for an end-of-treatment visit as soon as possible after discontinuation of the trial product and the two safety follow-up visits (7 and 30 days after the last dose of trial product). Once the follow-up visits were completed, a phone contact was made every 3 months to collect information on glucose-lowering treatment and any serious adverse events. These patients also attended a visit at week 104 to report glucose-lowering treatment and serious adverse events, and to have HbA_{1c} measured. Thus, once patients who met the primary endpoint of needing treatment intensification had permanently discontinued trial product, they were not withdrawn from the study.

Given the 2-year duration of this study, and the pragmatic frequency of patient visits, a global expert panel consisting of national investigators, national study coordinators, and sponsor representatives was established to provide expertise and input on study conduct, best clinical practice, recruitment, and retention.

Study participants

Patients included were aged 18 years and older, had been diagnosed with type 2 diabetes before the day of screening, had a HbA_{1c} of 7·0–11·0% (53–97 mmol/mol), a BMI of 20 kg/m² or higher, and were on stable daily doses of biguanides (metformin ≥1500 mg or maximum tolerated dose), sulphonylureas, glinides, pioglitazone, or dipeptidyl peptidase 4 inhibitors (DPP-4i; greater than or equal to half of the maximum approved dose according to local label or maximum tolerated dose). DPP-4i and glinides were not allowed as monotherapies or in combination with each other. Glinides were discontinued due to the increased risk of hypoglycaemia associated with concomitant use of glinides and insulin therapy. When the trial product (IDegLira or IGlar U100) was added to sulphonylurea therapy, a reduction in the dose of sulphonylurea could have been considered based on safety reasons, but otherwise those oral antidiabetic drugs were to be continued at the pre-trial dose. We followed a pragmatic principle and the decision was based on the discretion of the investigator.

Exclusion criteria included treatment with any medication for diabetes or obesity other than that stated in the inclusion criteria during 90 calendar days before screening, anticipated initiation or change in concomitant medications known to affect weight or glucose metabolism, and renal impairment (estimated glomerular filtration rate <60 mL/min/1·73 m²). Full inclusion and exclusion criteria are presented in the appendix (pp 2–3).

The trial was done in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice[29] and the Declaration of Helsinki.[30] Before the trial initiation, the protocol, the consent form, and the patient information sheet were reviewed and approved according to local regulations by appropriate health authorities, and by an independent ethics committee or institutional review board. The patients were informed of the risks and benefits of the trial, and that they could withdraw from the trial at any time for any reason. Consent was obtained in writing before or at visit 1 (screening), before commencing any trial-related activities.

Randomisation and masking

Patients were randomly assigned 1:1 to either IDegLira or IGlar U100, in combination with oral antidiabetic drugs, with the use of an interactive web response system and a simple sequential allocation randomisation schedule with block size of four. Treatment assignment was masked for an internal safety committee (responsible for safety surveillance), an independent external committee that adjudicated selected adverse events, 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 because it was not possible to provide masked treatment without limiting the maximum dose of IGlar U100.

Procedures

Patients were randomly assigned to receive either IDegLira (degludec 100 units/mL plus liraglutide 3·6 mg/mL, in a 3 mL prefilled PDS290 pen for subcutaneous injection) or IGlar U100 (insulin glargine 100 units/mL solution, in a 3 mL prefilled Solostar pen for subcutaneous injection), both administered once daily at any time of day, and it was recommended that the time of day remained the same throughout the trial.

Patients initiated IDegLira at 10 units, consisting of 10 units of degludec and 0·36 mg of liraglutide, or 10 units of IGlar U100. Dose was titrated twice a week by patients, to a fasting plasma glucose (FPG) target between 4·0 and 5·0 mmol/L (72–90 mg/dL) according to a titration algorithm (appendix p 4); however, it is important to note that monitoring of titration was not mandated between visits. The maximum dose of IDegLira was 50 units (50 units of degludec and 1·8 mg of liraglutide). IGlar U100 had no maximum dose. Patients continued pretrial oral antidiabetic drugs except for DPP-4i and glinides, which were discontinued at randomisation in both treatment groups.

Patients were provided with a blood glucose meter (Abbott Freestyle Precision Neo BG meter or Abbott Precision Xtra, depending on local availability [Abbott Diabetes Care, Abbott Park, IL, USA]) and were instructed on how to use the device. The blood glucose meters used test strips calibrated to plasma values. Therefore, all measurements performed with capillary blood were automatically calibrated to plasma equivalent glucose concentration values.

Outcome measures

The primary endpoint was time from randomisation to inadequate glycaemic control and need for treatment intensification, defined as HbA_{1c} of 7·0% (53 mmol/mol) or higher at two consecutive visits from week 26 (including week 26, if HbA_{1c} was ≥7·0% [<53 mmol/mol] at week 12), assessed up to and including 104 weeks. Patients withdrawing from the trial or discontinuing treatment (regardless of reason for discontinuation) contributed to the primary analysis as needing treatment intensification from the time of withdrawal or discontinuation.

Supportive secondary endpoints included change from baseline after 104 weeks of treatment in FPG, 9-point self-measured blood glucose (SMBG) profile, bodyweight, and insulin dose. Responder and composite endpoints included HbA_{1c} less than 7·0% (53 mmol/mol) after 104 weeks of treatment; HbA_{1c} <7·0% (<53 mmol/mol) without weight gain; HbA_{1c} <7·0% (<53 mmol/mol) without severe or blood glucose-confirmed symptomatic hypoglycaemic episodes during the last 12 weeks of treatment; and HbA_{1c} less than 7·0% (<53 mmol/mol) without weight gain and without severe or blood glucose-confirmed symptomatic hypoglycaemic episodes during the last 12 weeks of treatment. Other secondary endpoints included change from baseline after 104 weeks of treatment in blood pressure (systolic and diastolic), pulse rate, fasting lipid profile (cholesterol, low-density lipoprotein cholesterol [LDL cholesterol], high-density lipoprotein cholesterol [HDL cholesterol], very-low-density lipoprotein cholesterol [VLDL cholesterol], triglycerides, and free fatty acids). Supportive secondary safety endpoints included number of severe or blood glucose-confirmed symptomatic hypoglycaemic episodes and number of treatment-emergent adverse events during 104 weeks of treatment. A full list of endpoints can be found in the appendix (pp 5–6).

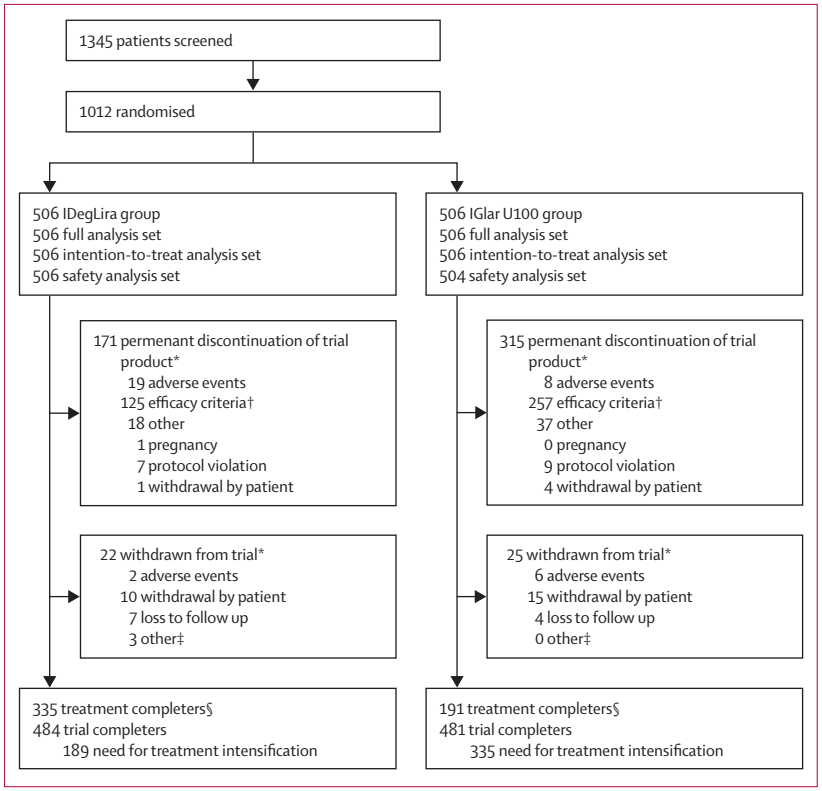

Figure 1: **Trial profile**
eCRF=electronic case report form. EOT=end of trial. IDegLira=insulin degludec. IGlar U100=insulin glargine 100 units/mL. *Before 104 week visit. †Reported as lack of efficacy on EOT form in eCRF. Patients that discontinued trial product before week 104 due to treatment intensification (primary endpoint) were reported on EOT form with reason lack of efficacy. ‡Other (IDegLira): fatal event, personal issues, duplicate patient. §Patients who completed week 104 visit without permanent discontinuation of trial product (patients who did not meet the primary endpoint of requiring treatment intensification in 104 weeks of treatment). Patients could be defined as needing treatment intensification also at week 104; six patients in the IGlar U100 group needed treatment intensification as a consequence of a missed visit or missing HbA_{1c}.

The definition of hypoglycaemia used (severe or blood glucose-confirmed symptomatic hypoglycaemia) included episodes that either required assistance from another person (severe) or were confirmed with a plasma glucose concentration of less than 3·1 mmol/L (56 mg/dL; blood glucose-confirmed) with symptoms consistent with hypoglycaemia (symptomatic). Hypoglycaemia was considered nocturnal if occurring between 00:01 and 05:59 h (both inclusive).

Patient-reported outcomes and safety and efficacy parameters at week 26 will be reported in separate publications, which are in development.

Statistical analyses

Based on experience from the phase 3a development programme for IDegLira and degludec, we assumed that about 45% of patients in the IDegLira group would need treatment intensification (including patients

withdrawing from the trial or discontinuing treatment) compared with about 55% in the IGlar U100 group during the 104-week treatment period. We required a total of 1000 patients (500 per treatment group) to achieve the primary objective with 90% power to detect a hazard ratio (HR) of 0·75 for IDegLira relative to IGlar U100 (ie, a 25% reduction in the hazard rate for needing treatment intensification over 104 weeks) using a two-group log-rank test and a two-sided significance level of α=0·05.

	IDegLira group (n=506)	IGlar U100 group (n=506)
Sex		
Male	280 (55%)	275 (54%)
Female	226 (45%)	231 (46%)
Age, years	56·8 (10·0)	56·4 (10·1)
Weight, kg	89·7 (20·5)	89·0 (20·1)
BMI, kg/m²	32·0 (6·2)	31·9 (5·8)
Duration of diabetes, years	10·0 (6·2)	10·2 (6·1)
HbA_{1c}, %	8·4% (1·0)	8·6% (1·0)
HbA_{1c}, mmol/mol	68·1 (11·4)	70·5 (10·9)
Fasting plasma glucose, mmol/L	9·9 (2·9)	10·2 (2·9)
Fasting plasma glucose, mg/dL	177·5 (52·8)	183·2 (51·4)
Oral antidiabetic drugs at screening		
Metformin	495 (98%)	494 (98%)
Sulphonylurea	320 (63%)	334 (66%)
Dipeptidyl peptidase 4 inhibitor*	171 (34%)	145 (29%)
Pioglitazone	38 (8%)	42 (8%)
Glinide*	7 (1%)	7 (1%)
α-glucosidase inhibitor	1 (<1%)	0

Data are n (%) or mean (SD), unless otherwise stated. Baseline refers to week 0. The duration of diabetes is calculated as the time from date of diagnosis to randomisation. IDegLira=insulin degludec plus liraglutide. IGlar U100=insulin glargine 100 units/mL. *Discontinued at randomisation.

Table 1: **Baseline characteristics**

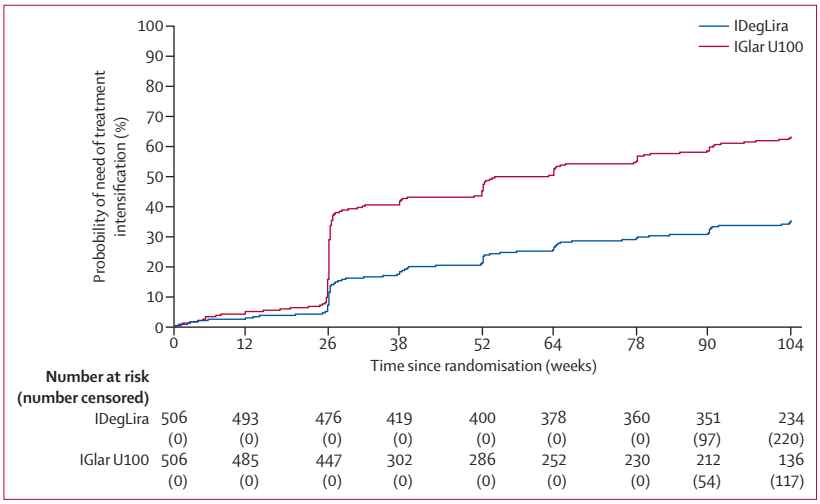

Figure 2: **Time to need for treatment intensification**
Need based on HbA_{1c} 7·0% or higher [53 mmol/mol] at two consecutive visits from week 26 onwards. Data based on full analysis set. Patients discontinuing treatment contributed to analyses as needing treatment intensification from time of discontinuation. IDegLira=insulin degludec plus liraglutide. IGlar U100=insulin glargine 100 units/mL.

We included all randomly assigned patients in the full analysis set and included all patients receiving at least one dose of trial product in the safety analysis set.

For the primary analysis, we followed the intention-to-treat principle. The estimand for the primary endpoint assessed the treatment effect on the time from randomisation to need for treatment intensification in all randomly assigned patients, regardless of reason for discontinuation of the trial product (appendix pp 7–8). We assessed the primary endpoint up to and including 104 weeks and analysed it using a stratified log-rank test in which treatment, baseline HbA_{1c} group (HbA_{1c} <8·5% [69 mmol/mol] or HbA_{1c} ≥8·5% [69 mmol/mol]), and previous oral antidiabetic drug treatment (sulphonylurea or no sulphonylurea) were included as strata in the model. We right-censored patients who completed the week 104 visit on-treatment, and who did not need treatment intensification, at time of visit. We imputed missing HbA_{1c} as HbA_{1c} of 7·0% (53 mmol/mol) or higher, for the derivation of the primary endpoint only. We did two sensitivity analyses; the first sensitivity analysis accounted for the interval censored nature of the data, with a proportional hazards regression model with piecewise constant baseline hazard for interval censored data. The second sensitivity analysis was a generalised log-rank test for interval censored time to treatment failure time, which compared the time to need for treatment intensification between patients given IDegLira or IGlar U100 with a two-sided non-parametric test at a 5% significance level.

We based the analysis of the 9-point SMBG profile on patients in the full analysis set who completed 104 weeks of treatment without need for treatment intensification using a mixed model for repeated measurements. We analysed change in bodyweight, insulin dose, FPG, and SMBG based on a trial product strategy using a mixed model for repeated measurements using the full analysis set, including all on-treatment values at planned scheduled visits. For continuous endpoints analysed at 104 weeks, the on-treatment estimand assessed the treatment effect for all randomly assigned patients under the assumption that all patients remained on trial product for the duration of the trial and did not need treatment intensification (appendix pp 7–8).

We also analysed hypoglycaemia endpoints using a trial product strategy using a negative binomial regression model with no imputation. For hypoglycaemia endpoints analysed at 104 weeks, the estimand assessed treatment effect in all randomly assigned patients, assuming patients remained on trial product for the entire planned duration of the trial and did not need treatment intensification (appendix pp 7–8).

We analysed the proportion of patients reaching HbA_{1c} of less than 7·0% (<53 mmol/mol) and composite responder endpoints using logistic regression. The

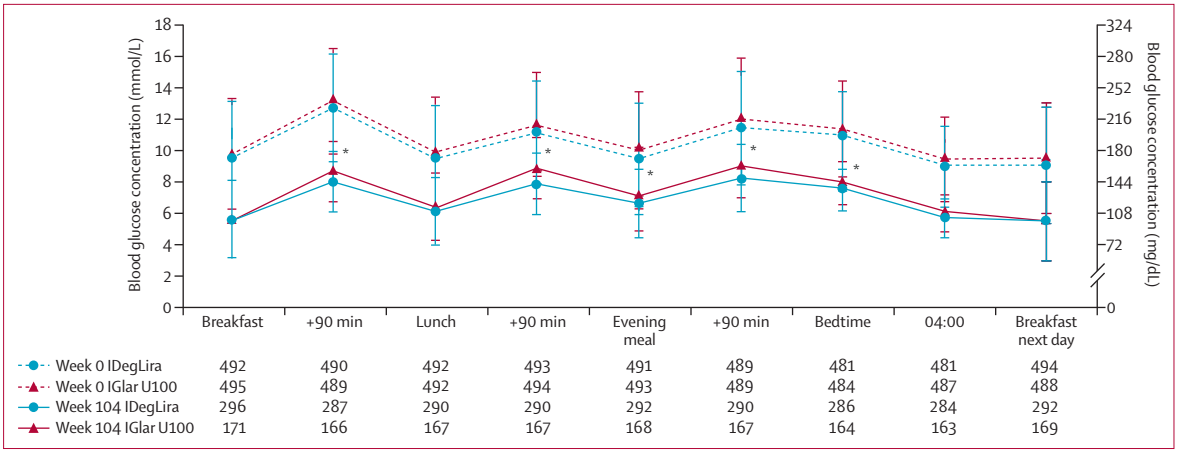

Figure 3: **9-point SMBG profile at week 0 and week 104**
Data are observed means and SD. IGlar U100=insulin glargine 100 units/mL. SMBG=self-measured blood glucose. *p<0·05. IDegLira=insulin degludec plus liraglutide.

estimand assessed the treatment effect for all randomly assigned patients considering discontinuation from trial product (regardless of reason) as a failure to respond to treatment (appendix pp 7–8). We imputed patients withdrawing from the trial or discontinuing treatment as non-responders from time of withdrawal or discontinuation. We imputed patients with missing values (HbA_{1c}, weight, or both) as non-responders at visits with missing values (HbA_{1c}, weight, or both). For hypoglycaemia endpoints, we imputed patients with less than 12 weeks of exposure as non-responders.

We did all statistical analyses as prespecified in the protocol. Post-hoc analyses of baseline characteristics and key efficacy parameters in patients who met the criterion for needing treatment intensification used descriptive statistics only. All analyses were done with SAS version 9.4 with analytical product SAS/STAT 14.3. This trial is registered with ClinicalTrials.gov, number NCT02501161.

Role of the funding source

Novo Nordisk funded the trial and was responsible for trial design and data analysis. All authors had full access to all data, were responsible for data interpretation and manuscript preparation, and had final responsibility for the decision to submit for publication.

Results

From Jan 8, 2016, to Oct 3, 2018, 1345 patients were screened and 1012 (75·2%) were randomly assigned to the IDegLira group (n=506) or the IGlar U100 group (n=506; figure 1). Two patients in the IGlar U100 group were never exposed to trial drug. 484 (96%) of 506 in the IDegLira group and 481 (95%) of 506 in the IGlar U100 group completed the trial (figure 1). Baseline characteristics were well matched between treatment groups (table 1). The estimands for all endpoints are summarised in the appendix (pp 7–8).

The time from randomisation to inadequate glycaemic control and need for treatment intensification was significantly longer for patients in the IDegLira group than those in the IGlar U100 group, accounting for baseline strata (baseline HbA_{1c} group and background sulphonylurea; p<0·0001, stratified log-rank test). The median time to treatment intensification was beyond 2 years for IDegLira and approximately 1 year for IGlar U100 (figure 2; appendix p 24).

Over 104 weeks, fewer patients in the IDegLira group (189 [37%] of 506) needed intensification than those in the IGlar U100 group (335 [66%] of 506). The most common reason for permanent discontinuation of trial product was lack of efficacy—ie, need for treatment intensification (125 [25%] of 506 in the IDegLira group and 257 [51%] of 506 in the IGlar U100 group)—as expected due to the trial design. Few patients discontinued for other reasons (figure 1).

The preplanned sensitivity analyses of the primary endpoint were in agreement with the primary analysis (HR 0·45 [95% CI 0·38–0·54] in the proportional hazards regression model and the generalised log-rank test was also in favour of IDegLira; p<0·0001; appendix pp 9–10).

A greater proportion of patients achieved HbA_{1c} of less than 7·0% (<53 mmol/mol) in the IDegLira group versus the IGlar U100 group (56% *vs* 29%; odds ratio 3·01 [95% CI 2·29–3·95]; p<0·0001). Additionally, a greater proportion of patients in the IDegLira group compared with the IGlar U100 group reached the composite endpoints of HbA_{1c} of less than 7·0% (<53 mmol/mol) without hypoglycaemia, HbA_{1c} of less than 7·0% (<53 mmol/mol) without weight gain, and HbA_{1c} of less than 7·0% (<53 mmol/mol) without hypoglycaemia and weight gain, and the estimated odds were significant and in favour of IDegLira for all these composite endpoints (appendix p 25). Results were similar when using an HbA_{1c} target of 6·5% (48 mmol/mol) or less (appendix p 25).

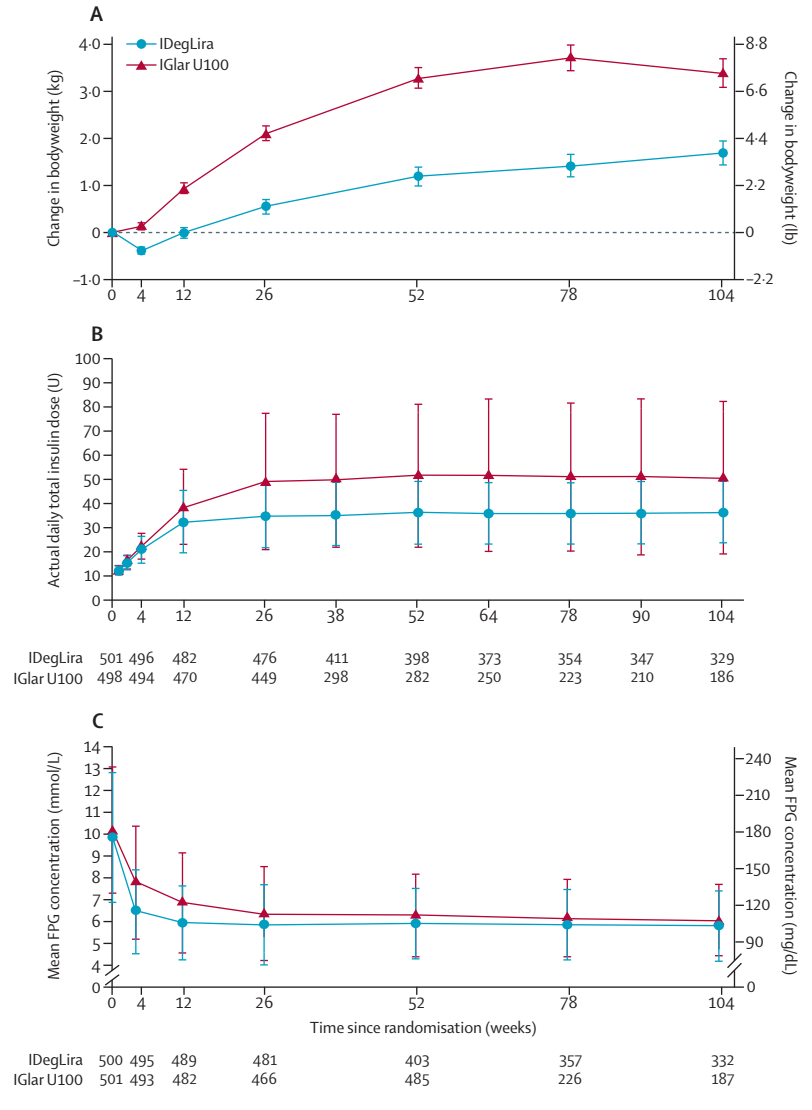

Figure 4: **Key secondary efficacy endpoints**
(A) LSMean (SE) change in bodyweight. (B) Mean (SD) observed daily total insulin dose. (C) Mean (SD) observed FPG over time. FPG=fasting plasma glucose. IDegLira=insulin degludec plus liraglutide. IGlar U100=insulin glargine 100 units/mL. LS=least squares.

Patients on treatment had similar reductions in observed mean fasting SMBG over 104 weeks of treatment with IDegLira and IGlar U100, with reductions being greater in the IDegLira group in the first 26 weeks of treatment (appendix p 26). For patients in the IDegLira group and still on treatment at week 104, mean SMBG was significantly lower than patients still receiving IGlar U100 treatment at five of the nine timepoints tested in the 9-point SMBG profile (90 min after breakfast, 90 min after lunch, before evening meal, 90 min after evening meal, and before bedtime). No significant difference was found in mean SMBG at other timepoints (figure 3; appendix p 11). The prandial increments overall (estimated treatment difference [ETD] –0·63 [95% CI –0·90 to –0·35]; p<0·0001), at breakfast (ETD –0·73 [–1·17 to –0·30]; p=0·0010), and lunch (ETD –0·71 [–1·15 to –0·26]; p=0·0018) were significantly lower in patients in the IDegLira group than those in the IGlar U100 group. No significant differences were found between treatment groups at the evening meal (ETD –0·42 [–0·86 to –0·02]).

After 104 weeks, bodyweight had increased in both treatment groups, but patients in the IDegLira group had significantly less weight gain than those in the IGlar U100 group (least squares means [LSMeans] +1·7 kg [SE 0·3] *vs* +3·4 kg [0·3]; ETD –1·70 [95% CI –2·47 to –0·93]; p<0·0001; figure 4A). Patients in the IDegLira group had a lower estimated mean total insulin dose than those in the IGlar U100 group after 104 weeks (LSMeans 37 U [0·8] *vs* 52 U [1·0]; ETD –14·94 [–17·41 to –12·47]; p<0·0001; figure 4B). From baseline to week 104, a significant reduction in FPG was shown in patients in the IDegLira group compared with the IGlar U100 group (ETD –0·48 [–0·76 to –0·19]; p=0·0010; figure 4C).

The estimated treatment ratio between IDegLira and IGlar U100 was not statistically different from 1.0 for either fasting C-peptide or fasting human insulin (appendix p 12).

Patients in the IDegLira group had a lower rate of severe or blood glucose-confirmed symptomatic hypoglycaemia compared with the IGlar U100 group (LSMeans 0·38 *vs* 0·86 events per patient-year of exposure [PYE]; estimated rate ratio [ERR] 0·44 [95% CI 0·33–0·60]; p<0·0001; figure 5; appendix p 13). Patients in the IDegLira group had a significantly lower rate of nocturnal hypoglycaemia compared with the IGlar U100 group (LSMeans 0·07 *vs* 0·22 events per PYE; ERR 0·32 [0·20–0·51]; p<0·0001).

Patients in the IDegLira group had a similar number of adverse events (217·4 *vs* 216·6 events per 100 PYE) and serious adverse events (12·8 *vs* 11·2 events per 100 PYE) to the IGlar U100 group. No new or unexpected safety and tolerability issues were identified (table 2; appendix p 14). Serious adverse events are presented by systems organ class and preferred term in the appendix (pp 15–18). A total of 55 adverse events led to dose reduction of trial product (31 in the IDegLira group and 24 in the IGlar U100 group) and, of these, three events (osteoarthritis, tympanoplasty and hypoglycaemia) in the IDegLira group and six events (cholecystitis infection and squamous cell carcinoma of skin in the same patient, osteoarthritis, cervicobrachial syndrome, pericarditis, and atrial fibrillation) in the IGlar U100 group were serious adverse events.

Pulse rate was significantly faster in patients in the IDegLira group (LSMean +2·1 beats per min [SE 0·4]) versus IGlar U100 (LSMean –0·6 beats per min [0·6]; ETD 2·70 [95% CI 1·31–4·09]; p<0·0001). The change in systolic blood pressure (LSMeans +0·34 mm Hg [0·69] in the IDegLira group *vs* +1·76 mmHg [0·88] in the IGlar U100 group) and diastolic blood pressure (LSMeans +0·15 mm Hg [0·42] *vs* +0·56 mm Hg [0·53]) from baseline to week 104 were not significant between groups.

No significant difference was found between patients in the IDegLira group and IGlar U100 group in the change from baseline to week 104 in total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol, or triglycerides. A small but significant increase (p=0·0278) was seen in free fatty acids in the IGlar U100 group compared with IDegLira from baseline to week 104 (ETD 0·91 [95% CI 0·84–0·99]).

Results of clinical evaluations and laboratory assessments after 104 weeks of treatment are shown in the appendix (pp 19–22).

Patients in the IDegLira group had 0·30 gastrointestinal adverse events per PYE compared with 0·20 in the IGlar U100 group. No confirmed adjudicated thyroid or pancreatitis treatment-emergent adverse events were reported.

Mean (SD) HbA_{1c} over time is presented in the appendix (p 27). Patients are included until needing treatment intensification.

In patients who met the criterion for needing treatment intensification, mean HbA_{1c} was 8·70% (SD 1·12; 72 mmol/mol [SD 12]) at baseline and 7·48% (0·89; 58 mmol/mol [10]) at the last available visit on treatment in the IDegLira group (N=189) and 8·80% (0·99; 73 mmol/mol [11]) at baseline and 7·82% (1·00; 62 mmol/mol [11]) at the last available visit on treatment in the IGlar U100 group (N=335). FPG was 10·12 mmol/L (3·17) at baseline and 7·27 mmol/L (2·39) at last available visit in the IDegLira group and was 10·36 mmol/L (2·97) at baseline and 7·55 mmol/L (2·74) at the last available visit in the IGlar U100 group. Last available total daily insulin dose was 35·99 U (14·05) in the IDegLira group and 50·85 U (30·76) and in the IGlar U100 group. In the IDegLira group, 70 (37%) of 189 of patients meeting the criterion for needing treatment intensification reached the maximum IDegLira dose at any time and 61 (32%) were at maximum dose at the last available visit.

Discussion

DUAL VIII is the first trial, to our knowledge, to investigate the durability of initial injectable therapy (basal insulin plus GLP-1RA versus basal insulin) in people with type 2 diabetes. It showed greater durability of IDegLira (defined as significantly longer time to need for treatment intensification) versus IGlar U100, accounting for baseline strata, in a population uncontrolled on oral antidiabetic drugs. Over 104 weeks, fewer patients in the IDegLira group met criteria for intensification (37% *vs* 66%), at a reduced hazard rate (0·45) compared with those in the IGlar U100 group. The median time to treatment intensification was beyond 2 years for IDegLira and approximately 1 year for IGlar U100. Among randomly assigned patients not reaching treatment intensification criteria, those in the IDegLira group had improved clinical outcomes, including reductions in 9-point SMBG, less bodyweight gain, lower daily insulin dose and a lower FPG, compared with those in the IGlar U100 group (estimands described in the appendix [pp 7–8]).

Patients in the IDegLira group were more likely to achieve the predefined composite endpoint of HbA_{1c} of less than 7·0% (53 mmol/mol) without weight gain than those in the IGlar U100 group, which is consistent with

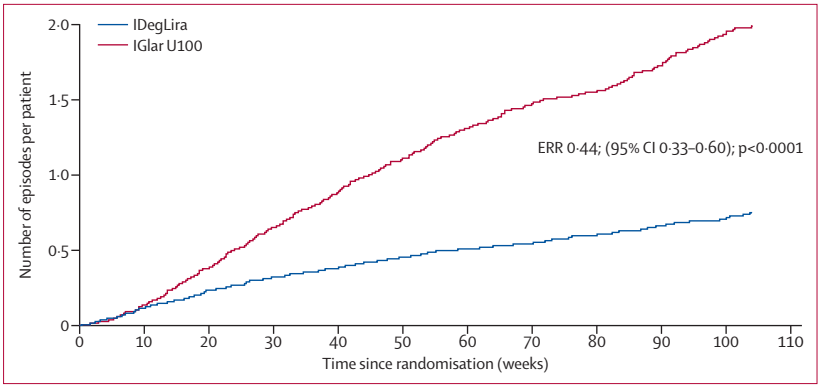

Figure 5: **Mean cumulative severe or blood glucose-confirmed symptomatic hypoglycaemic episodes over time**

The definition of hypoglycaemia used (severe or blood glucose-confirmed symptomatic hypoglycaemia) included episodes that either required assistance from another person (severe) or were confirmed with a plasma glucose concentration <3·1 mmol/L (56 mg/dL; blood glucose-confirmed) with symptoms consistent with hypoglycaemia. Hypoglycaemia endpoints were analysed with a negative binomial regression with no imputation. The treatment effect was assessed in all randomly assigned patients, assuming patients remained on trial product for the entire planned duration of the trial and did not need treatment intensification. ERR=estimated rate ratio. IDegLira=insulin degludec plus liraglutide. IGlar U100=insulin glargine 100 units/mL.

	IDegLira group (n=506)		IGlar U100 group (n=504)	
	Number of patients with one or more events (%)	Number of adverse events (rate*)	Number of patients with one or more events (%)	Number of adverse events (rate*)
Patient-years of exposure	822·55	..	631·60	..
Adverse events	384 (76%)†	1788 (217·4)	342 (68%)	1368 (216·6)
Serious	60 (12%)	105 (12·8)	43 (9%)	71 (11·2)
EAC-confirmed fatal	2 (<1%)	2 (0·2)	5 (1%)	6 (1·0)
Cardiovascular death	0	0	3 (1%)	3 (0·5)
Non-cardiovascular death	1 (<1%)	1 (0·1)	2 (<1%)	2 (0·3)
Undetermined	1 (<1%)	1 (0·1)	0	0
Mild	340 (67%)	1374 (167·0)	304 (60%)	981 (155·3)
Moderate	166 (33%)	360 (43·8)	151 (30%)	342 (54·1)
Severe	38 (8%)	53 (6·4)	30 (6%)	45 (7·1)
Adverse events leading to discontinuation of treatment	19 (4%)	24 (2·9)	7 (1%)	7 (1·1)
Adverse events leading to withdrawal	17 (3%)	22 (2·7)	4 (1%)	4 (0·6)
EAC-confirmed cardiovascular adverse events	13 (3%)	17 (2·1)	9 (2%)	15 (2·4)
EAC-confirmed neoplasm adverse events	7 (1%)	9 (1·1)	10 (2%)	12 (1·9)

EAC=event adjudication committee. IDegLira=insulin degludec plus liraglutide. IGlar U100=insulin glargine 100 units/mL. *Rate of events per 100 patient-years of exposure. †One adverse event in the IDegLira group was missing severity classification.

Table 2: **Treatment-emergent adverse events**

previous DUAL trials,[20,21,24,27] and is likely due to the insulin-sparing and beneficial weight effects of liraglutide. Additionally, patients in the IDegLira group had greater odds for achieving the composite endpoint of HbA_{1c} of less than 7·0% (53 mmol/mol) without hypoglycaemia versus those in the IGlar U100 group, which might be due to the insulin-sparing effect of liraglutide but might also be related to a lower incidence of hypoglycaemia reported with degludec than with IGlar U100.[31] Taken together, our findings provide evidence that patients who are in need of insulin therapy are more likely to reach a HbA_{1c} target of less than 7·0% (53 mmol/mol) with less weight gain and a lower incidence of hypoglycaemia when given a fixed ratio combination of basal insulin plus GLP-1RA (IDegLira) than with basal insulin alone (IGlar U100).

The greater durability seen with IDegLira might be related to the ability to target both fasting and postprandial hyperglycaemia compared with the use of basal insulin alone. Patients in the IDegLira group had an improved 9-point SMBG profile compared with patients in the IGlar U100 group, showing improved fasting and postprandial glycaemic control throughout the day. This outcome might be due to the complementary nature of degludec and liraglutide in addressing underlying distinct abnormalities of type 2 diabetes: basal insulins are effective at lowering HbA_{1c} and FPG, whereas liraglutide reduces FPG and postprandial glucose in a glucose-dependent manner.[32] Characteristics associated with durability versus drug failure could further support treatment decisions and future analyses to understand this distinction will be of interest.

A key driver of clinical inertia in type 2 diabetes is the challenge of adding to the existing polypharmacy of patients.[9] Weight gain and hypoglycaemia are also two major concerns for patients and health-care professionals when initiating insulin therapy, and these concerns contribute to clinical inertia, preventing patients from achieving glycaemic control.[33] Fear of injections and the burden of complex regimens also contribute to clinical inertia. Although both interventions in this study were once-daily injections, IDegLira showed improved outcomes compared with basal insulin alone, without the need for separate insulin and GLP-1RA injections, supporting the benefits of fixed ratio combination therapy. IDegLira has been shown to be safe when combined with metformin,[20–27] sodium-glucose co-transporter-2 inhibitors,[27] sulphonylureas,[23] and pioglitazone.[20] Together with the reported improvement in durability, weight benefit, and the lower incidence of hypoglycaemia compared with IGlar U100, initiating IDegLira might help reduce clinical inertia by helping to overcome the main barriers of achieving good glycaemic control when initiating insulin therapy. Clinical inertia associated with overbasalisation, defined as the continuous and inappropriate uptitration of basal insulin in an attempt to achieve glycaemic targets, can occur in patients poorly controlled on basal insulin, which in turn might increase their risk of weight gain and hypoglycaemia.[34] The early incorporation of a GLP-1RA during insulin initiation, as shown here with IDegLira, might prevent such overbasalisation.[34] Furthermore, a previous cost-effectiveness analysis identified that treatment with IDegLira versus continued uptitration of IGlar U100 shows a lower cost per patient achieving treatment targets.[35]

No apparent or unexpected safety or tolerability issues were found with IDegLira in this trial, and the safety profile was consistent with data from the previous DUAL trials.[20–27]

This trial had a high completion rate (about 95%) in both treatment groups for a study of long duration (2 years). It was designed to mirror recommended clinical practice[1,3] with titration guided solely by the physician, without external titration monitoring, and with fewer scheduled visits than might be expected of a treat-to-target clinical trial. The main limitation of the trial was the open-label design, but masking was not possible due to the maximum dose of IDegLira. This trial only investigated a single treatment choice, comparing durability of insulin-based therapies as the first injectable in the included population, and it did not investigate multiple combinations.

In conclusion, IDegLira showed greater durability than IGlar U100, in reaching and maintaining patients at glycaemic goals for longer, thereby minimising the need for additional therapy, while also reducing the side effects often associated with insulin-only therapy. Taken together, the data from DUAL VIII illustrate the potential benefit of a combined insulin plus GLP-1RA approach, such as IDegLira, as a first injectable therapy rather than insulin alone for patients with type 2 diabetes inadequately controlled on oral antidiabetic drugs.

Contributors

VRA served as the global signatory investigator for the trial and as such provided review, input, and approval of the study protocol before the start of the study, contributed to trial conduct, oversight, interpretation of the results, and to manuscript development and revision. RG, NH, and PŐ helped design the study. RG collected and analysed data. GG-G, MH, GJ, AK, MS, GS, RS, RG, NH, and PŐ interpreted the results and helped to develop and finalise the manuscript. All authors had full access to all data and had final responsibility for the decision to submit for publication.

Declaration of interests

VRA served as a consultant for Adocia, AstraZeneca BD, Novo Nordisk, Sanofi, Zafgen, and has received research support to her institution from Astra Zeneca–Bristol-Myers Squibb, Calibra, Eisai, Janssen, Novo Nordisk, Sanofi, and Theracos. PŐ, NH, and RG are employees and shareholders at Novo Nordisk. MH has been involved in various advisory boards and speaker panels for Novo Nordisk and was involved in multinational trials with Novo Nordisk products. GJ served as study investigator and has received honoraria for speaking engagements and for participation in advisory boards for Novo Nordisk. AK has been involved in various advisory boards for Abbott, Adcock Ingram, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Janssen Pharmaceuticals, Merck, Merck Sharp & Dohme, Mundipharma, Novartis, Novo Nordisk, Pfizer, and Sanofi, is a speaker panel member for Abbott, Aspen–GlaxoSmithKline, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Janssen Pharmaceuticals, Merck, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pharmplan, Pfizer, and Sanofi, and is

involved in research with AstraZeneca, Merck Sharp & Dohme, Novo Nordisk, and Pfizer. GS has received speaker or consulting honoraria from Novo Nordisk, Eli Lilly, AstraZeneca, Boehringer Ingelheim, Merck Sharp & Dohme, Sanofi, Amgen, Abbott, GlaxoSmithKline, and Servier. RS served as a consultant and speaker panel member for Novo Nordisk. GG-G reports personal fees from Novo Nordisk, Sanofi, Merck Sharp & Dohme, Amgen, Stendhal, AstraZeneca, Takeda, Abbott and Boehringer Ingelheim. All other authors declare no competing interests.

Data sharing

The patient-level analysis datasets for the research presented in the publication are available from the corresponding author on reasonable request.

Acknowledgments

We thank the patients who participated in this study, Kerry Guest, and Catherine Jones for writing and editing assistance.

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