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Original Investigation

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

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IMPORTANCE Achieving glycemic control remains a challenge for patients with type 2 diabetes, even with insulin therapy.

OBJECTIVE To assess whether a fixed ratio of insulin degludec/liraglutide was noninferior to continued titration of insulin glargine in patients with uncontrolled type 2 diabetes treated with insulin glargine and metformin.

DESIGN, SETTING, AND PARTICIPANTS Phase 3, multinational, multicenter, 26-week, randomized, open-label, 2-group, treat-to-target trial conducted at 75 centers in 10 countries from September 2013 to November 2014 among 557 patients with uncontrolled diabetes treated with glargine (20-50 U) and metformin (≥1500 mg/d) with glycated hemoglobin (HbA_{1c}) levels of 7% to 10% and a body mass index of 40 or lower.

INTERVENTIONS 1:1 randomization to degludec/liraglutide (n = 278; maximum dose, 50 U of degludec/1.8 mg of liraglutide) or glargine (n = 279; no maximum dose), with twice-weekly titration to a glucose target of 72 to 90 mg/dL.

MAIN OUTCOMES AND MEASURES Primary outcome measure was change in HbA_{1c} level after 26 weeks, with a noninferiority margin of 0.3% (upper bound of 95% CI, <0.3%). If noninferiority of degludec/liraglutide was achieved, secondary end points were tested for statistical superiority and included change in HbA_{1c} level, change in body weight, and rate of confirmed hypoglycemic episodes.

RESULTS Among 557 randomized patients (mean: age, 58.8 years; women, 49.7%), 92.5% of patients completed the trial and provided data at 26 weeks. Baseline HbA_{1c} level was 8.4% for the degludec/liraglutide group and 8.2% for the glargine group. HbA_{1c} level reduction was greater with degludec/liraglutide vs glargine (−1.81% for the degludec/liraglutide group vs −1.13% for the glargine group; estimated treatment difference [ETD], −0.59% [95% CI, −0.74% to −0.45%]), meeting criteria for noninferiority ($P < .001$), and also meeting criteria for statistical superiority ($P < .001$). Treatment with degludec/liraglutide was also associated with weight loss compared with weight gain with glargine (−1.4 kg for degludec/liraglutide vs 1.8 kg for glargine; ETD, −3.20 kg [95% CI, −3.77 to −2.64], $P < .001$) and fewer confirmed hypoglycemic episodes (episodes/patient-year exposure, 2.23 for degludec/liraglutide vs 5.05 for glargine; estimated rate ratio, 0.43 [95% CI, 0.30 to 0.61], $P < .001$). Overall and serious adverse event rates were similar in the 2 groups, except for more nonserious gastrointestinal adverse events reported with degludec/liraglutide (adverse events, 79 for degludec/liraglutide vs 18 for glargine).

CONCLUSIONS AND RELEVANCE Among patients with uncontrolled type 2 diabetes taking glargine and metformin, treatment with degludec/liraglutide compared with up-titration of glargine resulted in noninferior HbA_{1c} levels, with secondary analyses indicating greater HbA_{1c} level reduction after 26 weeks of treatment. Further studies are needed to assess longer-term efficacy and safety.

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Achieving optimal glucose control is a challenge for the majority of patients with type 2 diabetes, with less than one-third of patients treated with basal insulin reaching a glycated hemoglobin (HbA_{1c}) level of less than 7.0%.[1] Despite this, many patients continue basal insulin without treatment intensification.[2] Traditionally, such patients and their clinicians intensify the insulin regimen, generally by further up-titration of the basal insulin dose or with the addition of 1 or more mealtime insulin injections. Both options increase the risk of hypoglycemia and weight gain. In addition, there may be a practical limit to the glucose-lowering efficacy achievable with insulin titration alone, irrespective of the regimen. Recently, combinations of glucagon-like peptide-1 receptor agonists (GLP-1RAs) and basal insulin have been recommended as an alternative in international guidelines, extending the intensification options available.[3]

ETD *estimated treatment difference*

FPG *fasting plasma glucose*

GLP-1RA *glucagon-like peptide-1 receptor agonist*

PYE *patient-year of exposure*

SMBG *self-measured blood glucose*

In this trial, we addressed the practical and patient-centered question of the relative efficacy and safety of optimized and unlimited titration of a once-daily injection of basal insulin (glargine) vs a once-daily injection of the fixed-ratio combination of basal insulin degludec (dose limit of 50 U) and the GLP-1RA liraglutide (dose limit of 1.8 mg) (hereafter referred to as degludec/liraglutide). Although comparisons of degludec/liraglutide to more complex insulin regimens are being studied in an ongoing trial,[4] the use of basal insulin in combination with oral agents is the dominant treatment strategy for refractory hyperglycemia and the most relevant comparator for clinicians.

The primary objective of this trial was to determine whether degludec/liraglutide was noninferior to up-titration of glargine in change from baseline in HbA_{1c} level in patients with uncontrolled type 2 diabetes treated with glargine and metformin. If the primary objective was met, secondary objectives were to assess whether degludec/liraglutide was statistically superior compared with glargine in change from baseline of HbA_{1c} level, body weight, and rate of confirmed hypoglycemia.

Methods

The trial was reviewed and approved by institutional review boards, and all patients provided written, informed consent forms prior to participation. DUAL V was a phase 3, multinational, multicenter, randomized clinical trial conducted from September 2013 to November 2014 with a total length of 29 weeks (2 weeks from screening to randomization, 26-week treatment period, and 1 week posttreatment follow-up). This treat-to-target trial enrolled adults (aged ≥18 years) with type 2 diabetes with an HbA_{1c} level of 7% to 10% (inclusive), who were taking a stable dose of glargine (total daily dose, 20-50 U, inclusive, allowing individual fluctuations of ±10% for at least 56 days prior to screening), with stable daily dosing of metformin (≥1500 mg or maximum tolerated dose), body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of 40 or lower, and able to adhere to the protocol. The trial protocol and statistical analysis plan are available in Supplement 1.

Interventions

Patients were randomized 1:1 via an interactive voice/web response system to receive degludec/liraglutide or continued glargine, each treatment titrated to the same fasting glucose target. Patients randomized to degludec/liraglutide discontinued glargine and initiated degludec/liraglutide at 16 dose steps (16 U of degludec/0.6 mg of liraglutide), irrespective of the dose of glargine at the time of randomization, and dosed once daily at any time of day, preferably at the same time every day. The maximum allowed dose was 50 dose steps providing 50 U of degludec and 1.8 mg of liraglutide (the maximum dose of liraglutide approved for the type 2 diabetes indication).

Patients randomized to glargine continued treatment with their pretrial dosing, with no maximum daily dose during the trial period. Glargine was dosed once daily according to the locally approved prescribing information.

In both groups, target-driven titration was performed twice weekly based on the mean of 3 previous daily self-monitored prebreakfast blood glucose measurements. If this mean was above or below the 72 to 90 mg/dL target (to convert glucose to mmol/L, multiply by 0.0555), patients were to respectively increase or decrease their dose by 2 dose steps or 2 U.

Main Outcomes and Measures

The primary end point was change in HbA_{1c} level from baseline to 26 weeks. Secondary end points were change from baseline in body weight and number of treatment-emergent hypoglycemic episodes during 26 weeks. Exploratory prespecified end points included insulin dose, change from baseline in fasting plasma glucose (FPG) level, 9-point self-measured blood glucose (SMBG) profile, responders for HbA_{1c} level (predefined targets of <7.0% and ≤6.5%), and for composite targets based on HbA_{1c} level without hypoglycemia and/or without weight gain. Time points included in the 9-point SMBG profile were breakfast, 90 minutes after breakfast, lunch, 90 minutes after lunch, dinner, 90 minutes after dinner, bedtime, 4:00 AM, and breakfast the next day. Post-hoc analysis of mean blood glucose at each time point in the 9-point SMBG profile and analysis of confirmed hypoglycemia by end of treatment HbA_{1c} level were also performed. Safety end points included number of treatment-emergent adverse events and nocturnal hypoglycemic episodes during the 26-week treatment period, change from baseline in standard laboratory analyses (including lipid profile, amylase, lipase, and calcitonin), blood pressure, electrocardiogram, and pulse.

Confirmed hypoglycemic episodes were defined as episodes in which plasma glucose was biochemically confirmed as less than 56 mg/dL, with or without symptoms or in which the patient required assistance. A hypoglycemic episode was classified as severe if the patient required assistance, and nocturnal if it occurred between 12:01 AM and 05:59 AM (both inclusive). Patient-reported outcomes were measured using the Treatment-Related Impact Measure for Diabetes (TRIM-D) and 36-Item Short Form Survey (SF-36).

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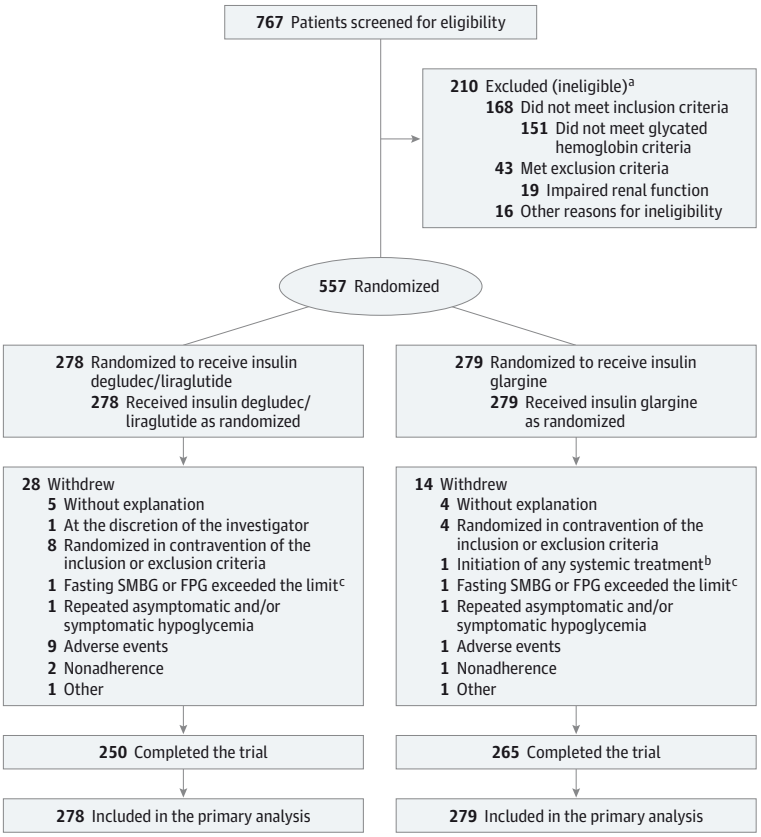
Figure 1. Flow of Patients Through the DUAL V Trial



FPG indicates fasting plasma glucose; SMBG, self-measured blood glucose.

[a] Patients could have more than 1 exclusion or inclusion criteria. Details only provided for criteria accounting for more than 5% screening failure rate.

[b] Initiation of any systemic treatment with products that, in the investigator's opinion, could interfere with glucose metabolism.

[c] Fasting SMBG or FPG limits leading to withdrawal were 270 mg/dL (to convert FPG to mmol/L, multiply by 0.0555) from baseline to week 6, 240 mg/dL from week 7 to week 12, and 200 mg/dL from week 13 to week 26.

Ethnicity and race were recorded to meet regulatory requirements and were self-reported by the participant from a predefined list.

All collected blood samples were processed and shipped immediately to a central laboratory (Quintiles), where all parameters were analyzed.

Statistical Analysis

The trial was powered to the primary objective of demonstrating noninferiority using a *t* test under the following assumptions: no treatment difference, a noninferiority margin of 0.3%, 1:1 randomization, nominal power of 90%, standard deviation of 1%, and 15% drop out. The noninferiority margin of 0.3% was selected based on existing US Food and Drug Administration (FDA) guidance, and is considered in the field the minimal clinically significant change for HbA_{1c} level.[5]

In total, 554 patients were planned to be randomized. The primary end point was analyzed using a standard analysis of covariance (ANCOVA) model, including treatment and region as fixed factors and baseline HbA_{1c} level as covariate. For secondary end points the family-wise type I error was controlled using 1-sided testing at the 2.5% level using the following prespecified test procedure that combines hierarchical testing and the Holm-Bonferroni method. First, the primary end point was tested for noninferiority using 1-sided testing at the 2.5% level. Second, if statistical significance was obtained, testing proceeded (hierarchical part) to the secondary end points. In turn, these end points were tested by the Holm-Bonferroni method comparing 1-sided *P* values against 2.5% significance levels adjusted for multiplicity.[6] Exploratory end points were tested 2-sided at the 5% level and not adjusted for multiplicity.

Continuous end points were analyzed by ANCOVA with treatment and region as fixed factors and corresponding baseline value as covariate (plus baseline HbA_{1c} level for dose); fasting lipid laboratory analyses were log-transformed prior to the analysis. The 9-point SMBG profile values were analyzed jointly using a linear mixed-model with an unstructured residual covariance matrix for measurements within patient and with treatment, time point, region, and interaction between treatment and time point as fixed effects and baseline 9-point SMBG profile values as covariates. Hypoglycemic episodes were analyzed using a negative binomial regression model with a log-link function and log of the exposure time as offset that included treatment and region as fixed factors. Responder end points (proportion of patients achieving HbA_{1c} level <7.0%, HbA_{1c} level ≤6.5%, and the composite end points described previously) were analyzed by a generalized linear model with binomial distribution and identity link that included treatment as a fixed factor. The choice of ANCOVA for continuous end points was based on European Medicines Agency (EMA)/FDA guidance and wide acceptance, and the negative binomial analysis of hypoglycemic events is widely accepted for diabetes trials.[5,7,8] Models were checked by residual plots and diagnostic statistics. Statistical analyses were based on the full

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analysis set (all randomized patients); efficacy and safety end point descriptive statistics are based on the full analysis set and safety analysis set (all patients receiving at least 1 dose of trial product), respectively (**Figure 1**). For the full analysis set analyses and descriptive statistics, a patient contributed with treatment "as randomized" (intention-to-treat principle). For safety analysis set descriptive statistics, a patient contributed with treatment "as treated" (principle of safety attributable to drug). In this particular trial, the 2 analysis sets are identical (ie, all randomized patients were exposed to their randomized treatment). Data are reported as mean (SD) unless otherwise noted. The estimated treatment differences (ETD) were calculated from the point estimates of the 2 treatments from the ANCOVA model (treatment factor levels) and associated standard error and covariance.

Sensitivity analyses were performed for secondary end points. For continuous end points (HbA_{1c} level and weight) repeated measures and 2 multiple imputation-based methods with sequential ANCOVAs were conducted.[9,10] Hypoglycemic episodes were analyzed by multiple imputation method using a posterior Bayesian approach.[11]

All statistical analyses were performed using SAS (SAS Institute), version 9.3.

Results

Patient Population

Patients from 10 countries were included, 767 were screened, and 557 were randomized and exposed to the trial products (Figure 1) from September 20, 2013, through November 4, 2014. Of the 557 patients randomized (mean: age 58.8 years; women, 49.7%), 92.5% completed the trial and provided data at 26 weeks. The treatment groups were comparable at baseline with respect to demographics and characteristics (**Table 1**). In total, 239 of 278 patients receiving degludec/liraglutide (86%) and 255 of 279 patients receiving glargine (91%) attended all scheduled visits from week 0 to 26.

Primary Objective

HbA_{1c} level decreased from baseline for the degludec/liraglutide group (8.4% [SD, 0.9%]) and glargine group (8.2% [SD, 0.9%]) over the first 16 weeks of treatment and stabilized at 6.6% for the degludec/liraglutide group (SD, 0.9%) and 7.1% for the glargine group (SD, 0.9%) by week 26. After 26 weeks of treatment, mean HbA_{1c} level had decreased by 1.81% for the degludec/liraglutide group (SD, 1.08%) and by 1.13% for the glargine group (SD, 0.98%) with glargine corresponding to an ETD of -0.59% (95% CI, -0.74% to -0.45%) (**Table 2** and **Figure 2**A), demonstrating noninferiority of degludec/liraglutide (upper bound of the 95% CI, -0.45%; less than the noninferiority margin of 0.3%, 1-sided *P* for noninferiority < .001) compared with glargine.

Secondary End Points

The ETD for change in HbA_{1c} level (-0.59% [95% CI, -0.74% to -0.45%], 1-sided *P* < .001) also met criteria for statistical superiority of degludec/liraglutide vs glargine (Table 2 and

Table 1. Baseline Demographics and Patient Characteristics of the Full Analysis Set

	Insulin Group, Mean (SD)	
	Degludec/ Liraglutide (n = 278)	Glargine (n = 279)
Women, No. (%)	135 (48.6)	142 (50.9)
Age, y	58.4 (9.8)	59.1 (9.3)
Race, No. (%)		
White	262 (94.2)	265 (95.0)
Black or African American	6 (2.2)	5 (1.8)
Asian	9 (3.2)	9 (3.2)
Other	1 (0.4)	0 (0.0)
Ethnicity, No. (%)		
Hispanic or Latino	107 (38.5)	133 (47.7)
Not Hispanic or Latino	171 (61.5)	146 (52.3)
Body weight, kg	88.3 (17.5)	87.3 (15.8)
BMI	31.7 (4.4)	31.7 (4.5)
Duration of diabetes, y	11.64 (7.44)	11.33 (6.59)
HbA_{1c}, %	8.4 (0.9)	8.2 (0.9)
Fasting plasma glucose, mg/dL	160.5 (47.5)	159.8 (52.0)
Basal insulin dose at screening, U	31 (10)	32 (10)
Vital parameters		
Pulse rate, beats/min[a]	74.9 (9.4)	74.0 (10.4)
Blood pressure, mm Hg		
Systolic	133.0 (13.8)	129.3 (13.8)
Diastolic	79.4 (8.4)	78.7 (8.3)
Concomitant illnesses, No. (%)		
Hypertension	209 (75.2)	194 (69.5)
Dyslipidemia	173 (62.2)	170 (60.9)
Laboratory measurements		
Total cholesterol, mg/dL	181.4 (41.2)	180.6 (44.5)
LDL-C, mg/dL	101.6 (35.8)	98.1 (35.0)
Free fatty acids, mg/dL	15.0 (5.90)	14.1 (6.52)
HDL-C, mg/dL	46.5 (10.9)	47.0 (12.2)
VLDL-C, mg/dL	33.22 (17.39)	35.33 (30.40)
Triglycerides, median (range), mg/dL	146.9 (36.3-1031.9)	140.7 (40.7-3790.3)
Lipase, U/L	41.7 (26.6)	43.3 (27.8)
Amylase, U/L	61.8 (43.0)	59.2 (29.1)
Calcitonin, median (range), pg/mL	1.0 (1.0-18.1)	1.0 (1.0-42.0)
Concomitant medication at screening, No. (%)[a]		
Statins	122 (43.9)	128 (45.9)
Fibrates	22 (7.9)	23 (8.2)
Other lipid-modifying drugs	5 (1.8)	4 (1.4)
Blockers of renin-angiotensin system	182 (65.5)	177 (63.4)
Calcium channel blockers	54 (19.4)	58 (20.8)
β-Blockers	74 (26.6)	83 (29.7)
Diuretics	25 (9.0)	19 (6.8)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very low–density lipoprotein cholesterol.

SI Conversion: To convert FPG to mmol/L, multiply by 0.0555; total cholesterol, HDL-C, and LDL-C to mmol/L, multiply by 0.0259; fatty acids to mmol/L, multiply by 0.0355; triglycerides to mmol/L, multiply by 0.0113; calcitonin to pmol/L, multiply by 0.292; amylase and lipase to μkat/L, multiply by 0.0167.

[a] Data were based on the safety analysis set.

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Table 2. Summary of Primary and Secondary End Points for Degludec/Liraglutide vs Glargine

End Point	Insulin Group		Degludec/Liraglutide vs Glargine[a]	1-Sided *P* Value
	Degludec/ Liraglutide (n = 278)	Glargine (n = 279)		
HbA_{1c} level at week 26, %	6.6	7.1		
Change from baseline in HbA_{1c} level, % (95% CI)	−1.81 (−1.94 to −1.68)	−1.13 (−1.25 to −1.02)	ETD (95% CI): −0.59 (−0.74 to −0.45)	Noninferiority: <.001 Superiority: <.001
Body weight at week 26, kg	86.9	89.1		
Change from baseline, body weight, kg (95% CI)	−1.4 (−1.8 to −1.0)	1.8 (1.4 to 2.2)	ETD (95% CI): −3.20 (−3.77 to −2.64)	Superiority: <.001
Total exposure, y	129.6	135.1		
Rate of confirmed hypoglycemia, no. of events per PYE	2.23	5.05	ERR (95% CI): 0.43 (0.30 to 0.61)	Superiority: <.001

Abbreviations: ERR, estimated rate ratio; ETD, estimated treatment difference; HbA_{1c}, glycated hemoglobin; PYE, patient-year of exposure.

[a] The ETD was estimated from an analysis of covariance analysis based on the full analysis set. The ERR was the ETD of the linear predictor of a negative binomial regression model, back transformed to event per time scale, based on the full analysis set.

Figure 2A). A reduction in body weight of 1.4 kg (SD, 3.5) was observed in the degludec/liraglutide group from 88.3 kg (SD, 17.5) to 86.9 kg (SD, 17.2), whereas the glargine group had an increase in body weight of 1.8 kg (SD, 3.6) from 87.3 kg (SD, 15.8) to 89.1 kg (SD, 15.9); ETD, -3.20 kg (95% CI, -3.77 to -2.64), 1-sided $P < .001$ (Table 2 and Figure 2B). Confirmed hypoglycemia occurred in fewer patients receiving degludec/liraglutide than those receiving glargine (28.4% for the degludec/liraglutide group and 49.1% for the glargine group), with reduced rates of 2.23 episodes vs 5.05 episodes per patient-year of exposure (PYE) (estimated rate ratio, 0.43 [95% CI, 0.30 to 0.61], 1-sided $P < .001$) (Table 2; Figure 2C). One severe hypoglycemic episode was reported in the trial, which was in the glargine group. Sensitivity analyses all demonstrated similar results in terms of statistical significance and effect sizes (eTable 1 in Supplement 2).

Exploratory Prespecified End Points

FPG level had decreased in both groups after 26 weeks of treatment to 109.5 mg/dL (SD, 38.4) for the degludec/liraglutide group and 110.2 mg/dL (SD, 38.6) for the glargine group; ETD, -0.15 mg/dL (95% CI, -6.28 to 5.99), $P = .96$ (**Figure 3**A). Mean SMBG levels measured for dose adjustment decreased in both groups over the first 12 weeks (more rapidly with degludec/liraglutide) and stabilized until week 26 at 105.8 mg/dL (SD, 26.0) for the degludec/liraglutide group and at 100.7 mg/dL (SD, 23.7) for the glargine group, as expected in a treat-to-target trial.

At week 26, the mean of the 9-point SMBG measurements had decreased in both groups, by 45.6 mg/dL (SD, 44.9) from baseline to 136.5 mg/dL (SD, 34.6) at 26 weeks for degludec/liraglutide and by 42.6 mg/dL (SD, 49.5) from baseline to 141.4 mg/dL (SD, 33.8) at 26 weeks for glargine. The between-group ETD was -4.0 mg/dL (95% CI, -9.6 to 1.6), $P = .16$ (Figure 3B).

More patients randomized to degludec/liraglutide achieved HbA_{1c} targets (specifically, <7.0% as well as ≤6.5%) than with glargine, and did so without weight gain and/or hypoglycemia ($P < .001$ for all) (**Table 3**).

In the glargine group, 24.4% of patients reported nocturnal confirmed hypoglycemic episodes, as did 6.1% in the degludec/liraglutide group, with event rates per PYE of 1.23 for the glargine group and 0.22 for the degludec/liraglutide group. The estimated rate ratio for nocturnal hypoglycemia was 0.17 (95% CI, 0.10 to 0.31), $P < .001$ (Figure 3C).

After 26 weeks, there were increases in the mean daily dose of degludec/liraglutide to 41 dose steps (41 U of degludec/1.48 mg of liraglutide) (range, 16-50) and to 66 U for glargine (range, 17-153) (Figure 3D). The between-group ETD insulin dose was -25.47 U (95% CI, -28.90 to -22.05), $P < .001$. Approximately 40% of patients in the degludec/liraglutide group received the maximum 50 dose steps after 26 weeks, of which 68% achieved an HbA_{1c} level less than 7% compared with 74% of those who used less than the maximum allowed degludec/liraglutide dose.

Patient-Reported Outcomes

The physical component score of the SF-36 questionnaire improved with degludec/liraglutide (from 47.4 [95% CI, 46.4 to 48.5] at baseline to 49.0 [95% CI, 48.0 to 50.0] at week 26) and worsened with glargine (from 47.7 [95% CI, 46.7 to 48.7] at baseline to 47.2 [95% CI, 46.1 to 48.3] at week 26); ETD, 1.9 [95% CI, 0.8 to 3.1], $P < .001$ (eTable 2 in Supplement 2). This was also the case with physical functioning (ETD, 1.4 [95% CI, 0.0 to 2.7], $P = .045$) and bodily pain (ETD, 2.0 [95% CI, 0.4 to 3.6], $P = .01$) subdomains; the general health subdomain score increased more with degludec/liraglutide (from 42.9 [95% CI, 41.9 to 44.0] at baseline to 46.2 [95% CI, 45.2 to 47.3] at week 26) than with glargine (from 43.6 [95% CI, 42.5 to 44.7] at baseline to 45.0 [95% CI, 43.9 to 46.1] at week 26; ETD, 1.7 [95% CI, 0.4 to 2.9], $P = .008$). There was no between-group difference in overall mental score (ETD, -0.1 [95% CI, -1.5 to 1.3], $P = .93$) or any component subdomains. Patient-reported outcome scores using the TRIM-D questionnaire improved in all subdomains and in total score in both groups. The increase in total score was greater with degludec/liraglutide (from 74.6 [95% CI, 73.1 to 76.2] at baseline to 82.1 [95% CI, 80.6 to 83.7] at week 26) compared with glargine (from 73.6 [95% CI, 72.1 to 75.1] at baseline to 78.9 [95% CI, 77.4 to 80.4] at week 26; ETD, 2.8 [95% CI, 0.9 to 4.7], $P = .003$), largely driven by higher scores than glargine in the treatment burden (ETD, 3.7 [95% CI, 0.7 to 6.8], $P = .02$) and diabetes management (ETD, 7.2 [95% CI, 4.2 to 10.2], $P < .001$) subdomains, indicating higher treatment satisfaction with degludec/liraglutide (eTable 2 in Supplement 2).

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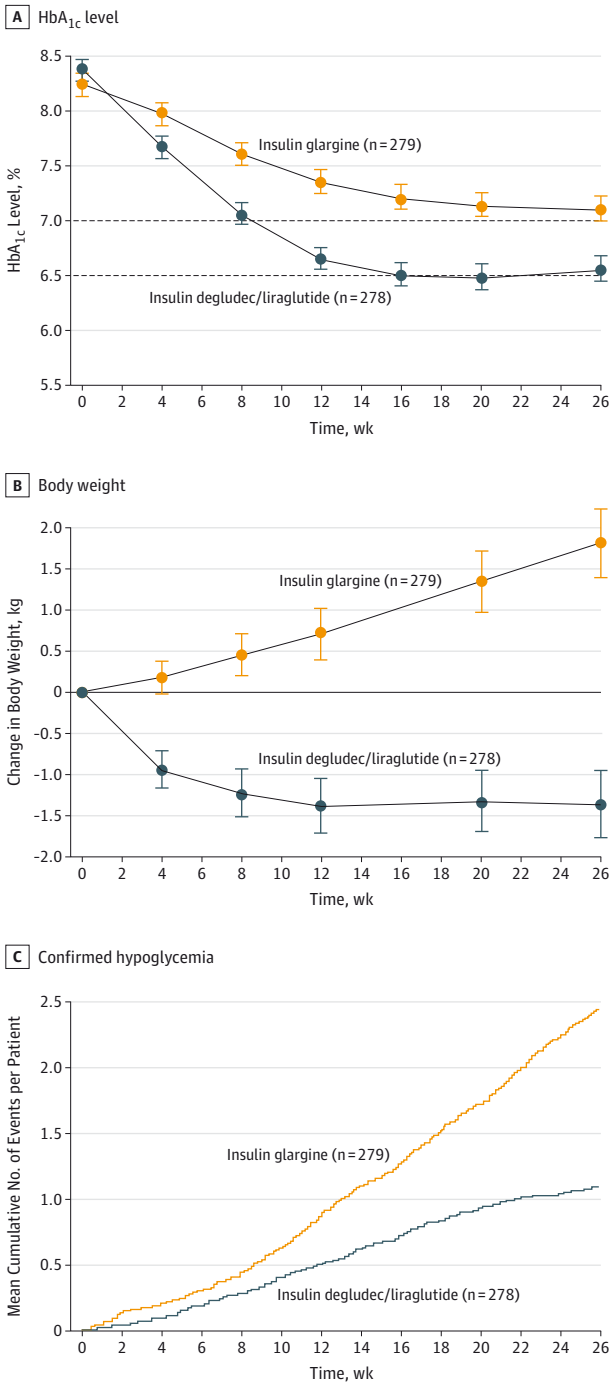
Figure 2. Change in HbA_{1c} Levels and Body Weight, and Cumulative Incidence of Confirmed Hypoglycemia Over Time for Degludec/Liraglutide vs Glargine



ANCOVA indicates analysis of covariance; HbA_{1c}, glycated hemoglobin. Time 0 indicates randomization. Error bars indicate 95% CIs. Panel A, The American Diabetes Association and European Association for the Study of Diabetes HbA_{1c} target was less than 7.0%; the American Association of Clinical Endocrinologists HbA_{1c} target was 6.5% or less (dashed lines). The estimated treatment difference (ETD) at 26 weeks was −0.59% (95% CI, −0.74% to −0.45%), $P < .001$ (1-sided, superiority), estimated from an ANCOVA analysis based on the full analysis set. Change in HbA_{1c} level for insulin degludec/liraglutide was −1.81; for insulin glargine, −1.13. B, The ETD at 26 weeks was −3.20 kg (95% CI, −3.77 to −2.64), $P < .001$ (1-sided, superiority), estimated from an ANCOVA analysis based on the full analysis set. Change in body weight for degludec/liraglutide was −1.4; for glargine, 1.8. A and B are based on observed values with missing data imputed by last observation carried forward for the full analysis set. C, Mean cumulative number of events per patient were based on the safety analysis set. The estimated rate ratio, 0.43 (95% CI, 0.30 to 0.61), $P < .001$ (1-sided, superiority), is the ETD of the linear predictor of a negative binomial regression model, back transformed to event per time scale, based on the full analysis set. The number of patients with 1 episode or more was 79 for degludec/liraglutide and 137 for glargine. There were 289 events, with a rate of 2.23 per patient-year of exposure for degludec/liraglutide and 683 events with a rate of 5.05 per patient-year of exposure for glargine.

Post Hoc Analyses

The lower rate of confirmed hypoglycemia observed with degludec/liraglutide compared with glargine was also seen irrespective of end-of-trial HbA_{1c} level (eFigure 1 in Supplement 2). Post hoc analysis of the 9-point SMBG measurements, using a linear mixed-model, showed a statistically significantly lower blood glucose level 90 minutes after lunch (ETD, -11.54 mg/dL [95% CI, -19.83 to -3.25], $P = .006$), before dinner (ETD, -12.48 mg/dL [95% CI, -20.05 to -4.92], $P = .001$), and after dinner (ETD, -10.24 mg/dL [95% CI, -19.45 to -1.02], $P = .03$), but a higher blood glucose level before breakfast (ETD, 8.28 mg/dL [95% CI, 2.98 to 13.59], $P = .002$) and before breakfast on the following day (ETD, 7.23 mg/dL [95% CI, 1.42 to 13.04], $P = .02$) for degludec/liraglutide than with glargine; blood glucose levels were similar at the other 4 time points.

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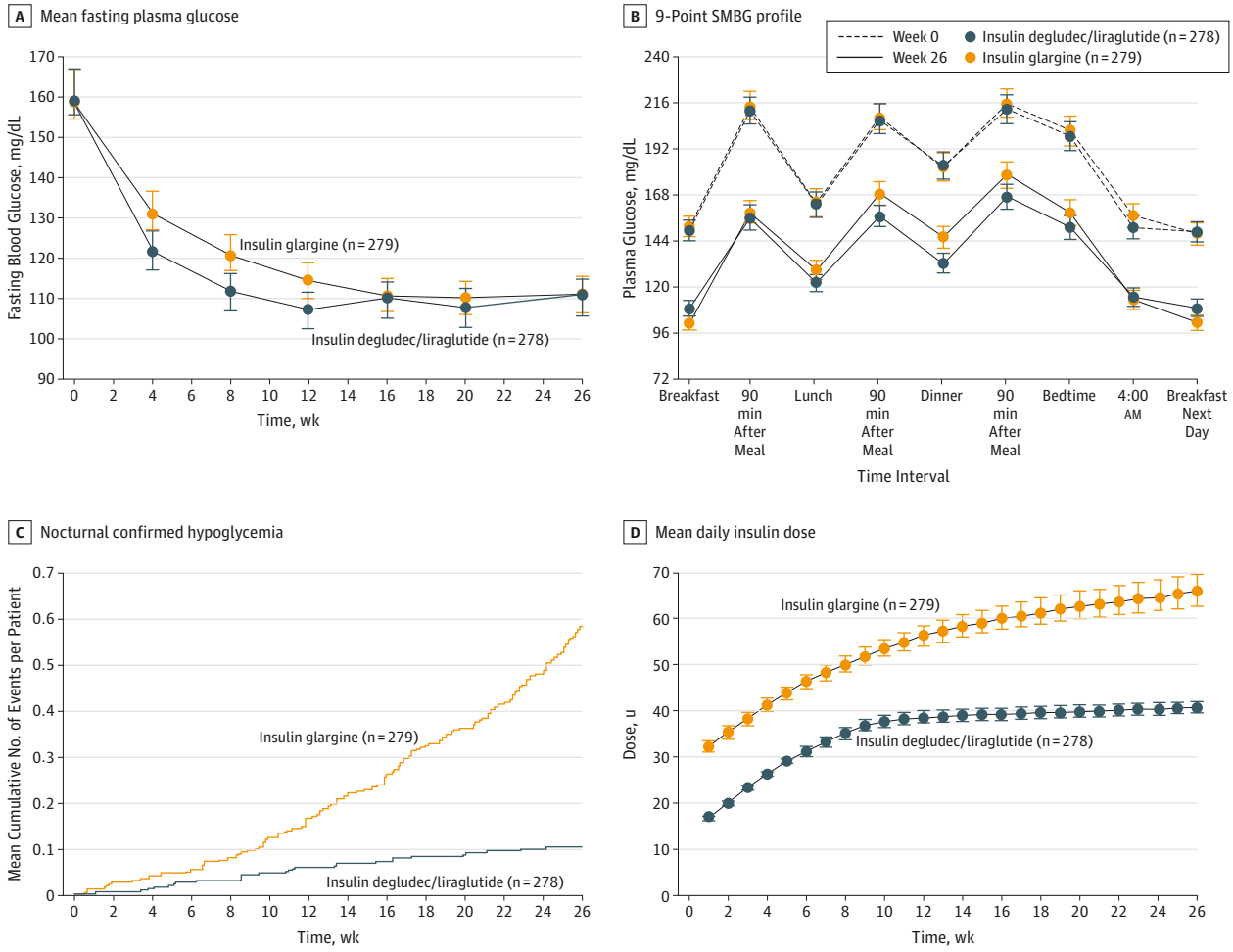
Figure 3. Change in Fasting Plasma Glucose, 9-Point SMBG Profile, Nocturnal Hypoglycemia, and Insulin Dose Over Time for Degludec/Liraglutide vs Glargine



ANCOVA indicates analysis of covariance; SMBG, self-measured blood glucose. To convert glucose to mmol/L, multiply by 0.0555. Time 0 indicates randomization. Error bars indicate 95% CIs. A, Based on observed values with missing data imputed by last observation carried forward for the full analysis set. The estimated treatment difference (ETD) at 26 weeks was −0.015 mg/dL (95% CI, −6.28 to 5.99), $P = .96$, estimated from an ANCOVA analysis based on the full analysis set. Change in mean fasting blood glucose for insulin degludec/liraglutide was −50.9 mg/dL; for insulin glargine, −49.9 mg/dL. B, Mean observed values were based on the full analysis set and missing values were imputed by last observation carried forward. At week 26, for breakfast, 90 minutes after lunch, dinner, 90 minutes after dinner, and breakfast the next day, $P < .05$ for degludec/liraglutide vs glargine based on linear mixed-model with an unstructured residual covariance matrix. C, Mean cumulative number of events per patient were based on the safety analysis set. The estimated rate ratio, 0.17 (95% CI, 0.10 to 0.31), $P < .001$, is the ETD of the linear predictor of a negative binomial regression model, back transformed to event per time scale, based on the full analysis set. Nocturnal was defined as between 12:01 AM to 5:59 AM (both inclusive). The number of patients with 1 episode or more was 17 for degludec/liraglutide and 68 for glargine. There were 29 events, with a rate of 0.22 per patient-year of exposure for degludec/liraglutide and 166 events with a rate of 1.23 per patient-year of exposure for glargine. D, Based on observed values with missing data imputed by last observation carried forward for the safety analysis set. The ETD at week 26 was −25.47 U (95% CI, −28.90 to −22.05), $P < .001$, estimated from an ANCOVA analysis based on the full analysis set. The degludec/liraglutide dose was capped at 50 dose steps; there was no maximum dose for glargine.

Vital Parameters

After 26 weeks of treatment, heart rate increased in the degludec/liraglutide group and remained similar to baseline with glargine (ETD, 3.71 beats/min [95% CI, 2.33 to 5.08], $P < .001$). Systolic blood pressure decreased with degludec/liraglutide and remained unchanged with glargine (ETD, −3.57 mm Hg [95% CI, −5.54 to −1.59], $P < .001$). There was no difference in the change in diastolic blood pressure between the groups (ETD, 0.91 mm Hg [95% CI, −0.28 to 2.10], $P = .14$), which remained similar to baseline (eTable 3 in Supplement 2).

Laboratory Measurements

After 26 weeks of treatment, total cholesterol (estimated treatment ratio [ETR], 0.95 [95% CI, 0.92 to 0.98], $P < .001$), low-density lipoprotein cholesterol (ETR, 0.92 [95% CI, 0.88 to 0.97], $P < .001$) and free fatty acids (ETR, 0.85 [95% CI, 0.80 to 0.92], $P < .001$) were lower with degludec/liraglutide than with glargine. No differences were observed for high-density lipoprotein, very low-density lipoprotein, and triglycerides between the groups at the end of trial.

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Table 3. Proportion of Patients Achieving HbA_{1c} and Composite Targets

	Insulin, No. (%)[a]			
	Degludec/ Liraglutide	Glargine	Between-Group Treatment Difference, % (95% CI)[b]	*P* Value
HbA_{1c} level <7%	199 (71.6)	131 (47.0)	24.6 (16.7-32.5)	<.001
No weight gain	139 (50.0)	55 (19.7)	30.3 (22.8-37.8)	<.001
No hypoglycemic episodes	151 (54.3)	82 (29.4)	24.9 (17.0-32.9)	<.001
No weight gain, no hypoglycemic episodes	108 (38.8)	34 (12.2)	26.7 (19.8-33.6)	<.001
HbA_{1c} level ≤6.5%	154 (55.4)	86 (30.8)	24.6 (16.6-32.5)	<.001
No weight gain	116 (41.7)	35 (12.5)	29.2 (22.2-36.2)	<.001
No hypoglycemic episodes	115 (41.4)	53 (19.0)	22.4 (15.0-29.8)	<.001
No weight gain, no hypoglycemic episodes	88 (31.7)	21 (7.5)	24.1 (17.8-30.4)	<.001

Abbreviations: HbA_{1c}, glycated hemoglobin.

[a] Responders were based on the full analysis set and last observation carried forward imputed data.

[b] Treatment differences were from a generalized linear model with binomial distribution and identity link and treatment as a factor.

There were increases in mean lipase (17.6 U/L [SD, 37.0]; to convert to µkat/L, multiply by 0.0167) and amylase (10.7 U/L [SD, 22.1]; to convert to µkat/L, multiply by 0.0167) activity during the treatment period in the degludec/liraglutide group and minimal change in the glargine group (-2.2 U/L [SD, 29.2] for lipase and 2.2 U/L [SD, 18.4] for amylase).

Calcitonin levels were similar between the degludec/liraglutide and glargine groups throughout the trial and there was no clinically relevant change from baseline at week 26 in either group: median change from baseline 0.0 pg/mL (range, -3.4-47.7) for the degludec/liraglutide group and 0.0 pg/mL (range, -20.5-8.0) for the glargine group (to convert to pmol/L, multiply by 0.292).

Adverse Events

The overall rate of adverse events per 100 PYE was 343.3 for the degludec/liraglutide group and 286.4 for the glargine group. Serious adverse events per 100 PYE were 3.9 for the degludec/liraglutide group and 6.7 for the glargine group. The majority of adverse events were mild and judged to be unlikely related to the trial products by the investigator. A higher proportion of adverse events were judged related to the trial product in the degludec/liraglutide group, these were mainly gastrointestinal disorders. Accordingly, nausea was reported by more patients in the degludec/liraglutide group (9.4%; n = 26; 26.2 events per 100 PYE) than the glargine group (1.1%; n = 3; 2.2 events per 100 PYE). However, no more than 4% of patients experienced nausea with degludec/liraglutide at any given week during the trial (eFigure 2 in Supplement 2).

Of 5 cardiovascular events sent for adjudication, 4 were confirmed by the external blinded event adjudication committee, 2 of which were major cardiovascular events (defined as nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death) (1 in each group). A patient treated with glargine died of hemorrhagic stroke, and a patient treated with degludec/liraglutide had an ischemic stroke followed by full recovery. Both events were considered unlikely related to the trial product by the investigator. Seven potential events of neoplasm were sent to the event adjudication committee for adjudication; 3 were confirmed (rectal adenocarcinoma, prostate cancer, and metastatic pancreatic carcinoma; the latter diagnosed 9 days after stopping treatment [day 54 of the trial]), all in the degludec/liraglutide group and all considered unlikely related to the trial product by the investigator. Two thyroid disease events were sent for adjudication; neither were confirmed as thyroid neoplasms. The single event of pancreatitis sent for adjudication was not confirmed by the event adjudication committee.

Discussion

Among patients with uncontrolled type 2 diabetes treated with glargine and metformin, degludec/liraglutide achieved noninferior HbA_{1c} level reduction (primary objective), and subsequently statistically greater HbA_{1c} level reduction (secondary objective) compared with continued glargine titration, when both products were titrated to the same fasting glycemic target. Further analyses demonstrated that degludec/liraglutide was associated with weight loss compared with weight gain with glargine and a lower rate of hypoglycemia.

Despite the initial reduction in insulin dose for patients randomized to the degludec/liraglutide group, from a mean of 31 U to 16 dose steps (including a liraglutide component of 0.6 mg), there was no deterioration in mean SMBG measurement immediately following this switch. The mean SMBG measurement decrease following randomization was greater in the degludec/liraglutide group, indicating a faster therapeutic response to degludec/liraglutide initiation compared with glargine up-titration. The maximum allowed dose of degludec/liraglutide was 50 dose steps, whereas there was no predefined maximum daily dose of glargine. Despite the dosing cap, a statistically and clinically significantly greater HbA_{1c} level reduction was achieved in the degludec/liraglutide group compared with the glargine group (final dose 41 U in the degludec/liraglutide group vs 66 U in the glargine group). The majority of patients treated with degludec/liraglutide met the less than 7.0% and 6.5% or less HbA_{1c} level targets, more than those in the glargine group, with a lower rate of hypoglycemia. These findings highlight the therapeutic benefits of the liraglutide component and its insulin-sparing effect.

The combination of basal insulin and GLP-1RA as a treatment option is well established.[3,12] Concern about hypoglycemia is a barrier to good glycemic control, rendering patients unwilling to optimize treatment with insulin[13] and clinicians reticent to recommend more aggressive treatment targets.[14] The burden of treatment complexity[13,14] and con-

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cerns about weight gain[15] may contribute to poor patient adherence to treatment intensification.[16] Equally, physicians cite lack of experience and time to educate patients as a barrier to initiating, modifying, and intensifying insulin treatment.[17] As a once daily, single injection that is effective, associated with weight loss, and a low risk of hypoglycemia, degludec/liraglutide may overcome many of the barriers to treatment intensification in patients treated with basal insulin. This suggestion is supported by the patient-reported outcome results.

Gastrointestinal complications are well-known adverse effects of treatment with GLP-1RA.[18] In the liraglutide clinical development program, nausea was reported by between 14% and 40% of patients treated with 1.2 mg and 1.8 mg of liraglutide compared with glargine and placebo.[19,20] In this trial, a lower proportion of patients treated with degludec/liraglutide reported 1 or more episodes of nausea (9.4%). This is likely due to a more gradual titration regimen for degludec/liraglutide compared with that customarily used for liraglutide (0.6 mg weekly). The liraglutide component in degludec/liraglutide is up-titrated in smaller increments (up to 0.072 mg twice weekly) with the titration scheme used, contributing to the tolerability of the product. The open-label nature of this trial could have introduced an unconscious bias resulting in overreporting of these events, as even fewer patients reported nausea (6.5%) in a double-blinded trial comparing degludec/liraglutide with insulin degludec.[21]

This study had several important limitations. It was necessary to perform the trial with an open-label design as the maximum dose of degludec/liraglutide was 50 dose steps and otherwise a double-dummy design would have been required with patients administering 2 injections daily in unlabeled syringes. The open-label nature of the trial may have biased reporting of adverse events by investigators or patient-reported outcomes scoring by patients. However, the event adjudication committee, who adjudicated cardiovascular, neoplasm, thyroid disease, or pancreatitis events were blinded to randomized treatment. The clinical applicability of this trial is limited to those who fit the inclusion and exclusion criteria. In clinical practice, this means that care must be taken to avoid extrapolating expectations from these results to patients with diabetes who were, for example, previously uncontrolled on a higher dose of basal insulin (ie, >50 U) or basal insulin in combination with therapies other than metformin. Though the fasting glucose level achieved by study end is similar between groups and to other treat to target trials and though the differences of rates of hypoglycemia were substantial, the mean glargine dose did not reach a plateau at study end; this does raise the possibility that with longer treatment duration or alternative insulin regimens differences in HbA_{1c} level may have been minimized, but at the expense of greater differences in hypoglycemia and weight gain.

Further research is indicated to evaluate the durability of the effects of degludec/liraglutide in longer-term studies, in clinical practice, and to assess whether patients and physicians consider degludec/liraglutide a suitable treatment option to overcome barriers to treatment intensification.

Conclusions

Among patients with uncontrolled type 2 diabetes taking glargine and metformin, treatment with degludec/liraglutide compared with up-titration of glargine resulted in noninferior HbA_{1c} levels, with secondary analyses indicating greater HbA_{1c} level reduction after 26 weeks of treatment. Further studies are needed to assess longer-term efficacy and safety.

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