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Effect of insulin degludec versus insulin glargine U100 on time in range: SWITCH PRO, a crossover study of basal insulin-treated adults with type 2 diabetes and risk factors for hypoglycaemia

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Abstract

Aims: To compare time in range (TIR) with use of insulin degludec U100 (degludec) versus insulin glargine U100 (glargine U100) in people with type 2 diabetes.

Materials and Methods: We conducted a randomized, crossover, multicentre trial comparing degludec and glargine U100 in basal insulin-treated adults with type 2 diabetes and ≥1 hypoglycaemia risk factor. There were two treatment periods, each with 16-week titration and 2-week maintenance phases (with evaluation of glucose using blinded professional continuous glucose monitoring). The once-weekly titration (target: 3.9–5.0 mmol/L) was based on pre-breakfast self-measured blood glucose. The primary endpoint was percentage of TIR (3.9—10.0 mmol/L). Secondary endpoints included overall and nocturnal percentage of time in tight glycaemic range (3.9–7.8 mmol/L), and mean glycated haemoglobin (HbA1c) and glucose levels.

Results: At baseline, participants (n = 498) had a mean (SD) age of 62.8 (9.8) years, a diabetes duration of 15.1 (7.7) years and an HbA1c level of 59.6 (11.0) mmol/mol (7.6 [1.0]%). Noninferiority and superiority were confirmed for degludec versus glargine U100 for the primary endpoint, with a mean TIR of 72.1% for degludec versus 70.7% for glargine U100 (estimated treatment difference [ETD] 1.43% [95% confidence interval (CI): 0.12, 2.74; $P = 0.03$] or 20.6 min/d). Overall time in tight glycaemic range favoured degludec versus glargine U100 (ETD 1.5% [95% CI: 0.15, 2.89] or 21.9 min/d). Degludec also reduced nocturnal time below range (TBR; <3.9 mmol/L) compared with glargine U100 (ETD −0.88% [95% CI: −1.34, −0.42] or 12.7 min/night; *post hoc*) and significantly fewer nocturnal hypoglycaemic episodes of <3.0 mmol/L were observed.

* Trial registration: ClinicalTrials.gov, NCT03687827.

Conclusions: Degludec, compared with glargine U100, provided more TIR and time in tight glycaemic range, and reduced nocturnal TBR in insulin-treated people with type 2 diabetes.

KEYWORDS
basal insulins, insulin analogues, insulin treatment, long-acting basal insulin, professional CGM, type 2

1 | INTRODUCTION

Maintaining tight glycaemic control reduces the risk of long-term complications in type 2 diabetes. Glycated haemoglobin (HbA1c) is considered a primary assessment for the diagnosis and glycaemic management of diabetes.[1] However, HbA1c measurements do not reflect the day-to-day fluctuations of blood glucose levels in people with diabetes,[2,3] who may experience hyperglycaemia and hypoglycaemia, yet still display HbA1c levels in the target range. Furthermore, due to variable red blood cell lifespans and glycation rates,[4] HbA1c measurements may not be reflective of glycaemic control in certain populations.

Improvements have been made in the accuracy and ease of measuring glucose and monitoring glycaemic control with continuous glucose monitoring (CGM) devices, which measure glucose levels within interstitial fluid and provide a dynamic understanding of changes. With CGM, time spent per day within (TIR), below (TBR) and above (TAR) target blood glucose range can also be calculated.[5] Increased TIR correlates with lower HbA1c measurements;[6] however, CGM enables more frequent monitoring, which can potentially detect more episodes of hypoglycaemia, and may support a safer achievement of glycaemic targets for people with diabetes treated with insulin.[7-10]

Insulin degludec (degludec; 100 U/mL) is a basal insulin analogue with a longer duration of action and comparatively lower risk of hypoglycaemia than earlier basal insulin analogues in people with type 1 or type 2 diabetes.[11-16] Parallel-group phase III trials demonstrated similar glycaemic control according to HbA1c measurement, and consistently lower hypoglycaemia risk with degludec compared with insulin glargine U100 (glargine U100; 100 U/mL).[11-14] The subsequent SWITCH 1 and SWITCH 2 studies (in type 1 and type 2 diabetes, respectively) further explored and confirmed the reduced relative risk of hypoglycaemia, despite an equivalent HbA1c, using a crossover design.[15,16] However, it has not been shown whether these findings reflect differences in TIR, TBR and TAR—metrics that more directly and thoroughly capture dynamic daily glucose levels using CGM.

The objective of the present phase IV study (SWITCH PRO; NCT03687827) was to compare the effect of degludec versus glargine U100 on glycaemic control using a design based on SWITCH 2, with the addition of blinded professional CGM to specifically characterize time spent in different glycaemic ranges, and glycaemic variability. Although insulin glargine U300 has an improved pharmacokinetic profile,[17] glargine U100 was chosen as the comparator for consistency with the degludec phase III clinical trial programme and SWITCH 2. It was anticipated that this would enable better illustration of the differences in CGM-driven new metrics of glycaemic control. It was also felt that any differences seen in TIR, TBR and TAR may better explain the previously observed differences in hypoglycaemia risk. The primary outcome was TIR, with secondary endpoints including overall and nocturnal time in tight glycaemic range, in insulin-treated adults with type 2 diabetes and risk factors for hypoglycaemia.

2 | MATERIALS AND METHODS

2.1 | Trial design

This 41-week, randomized, crossover, open-label, multicentre, active-controlled trial compared the effect of degludec (Novo Nordisk A/S, Bagsværd, Denmark) versus glargine U100 (Sanofi-Aventis, Paris, France), with or without oral antidiabetic drugs (OADs), in adults with type 2 diabetes using blinded professional CGM (Figure 1). The trial was conducted, in accordance with ethical principles derived from international guidelines including the Declaration of Helsinki[18] and the International Conference on Harmonisation Good Clinical Practice,[19] across 67 sites in five countries (United States, Canada, Poland, South Africa and Slovakia) between October 2, 2018 and December 27, 2019. All participants gave their informed consent prior to inclusion in the study.

2.2 | Study population

Study participants were aged ≥18 years with a diagnosis of type 2 diabetes ≥180 days prior to screening. Eligible participants had been treated with any basal insulin ≥90 days prior to screening, with or without OADs (metformin, dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter-2 inhibitors, alpha-glucosidase-inhibitors and thiazolidinediones). Sulphonylureas were excluded because of their association with increased risk of hypoglycaemia. Glucagon-like peptide-1 (GLP-1) receptor agonists were excluded to match the study population as closely as possible to that of the SWITCH 2 study, so that the decreased risk of hypoglycaemic events seen in SWITCH 2 could be evaluated further using CGM. Participants had an HbA1c level ≤80 mmol/mol (9.5%) at screening (confirmed by central laboratory analysis) and a body mass index (BMI) of ≤45 kg/m^2. They

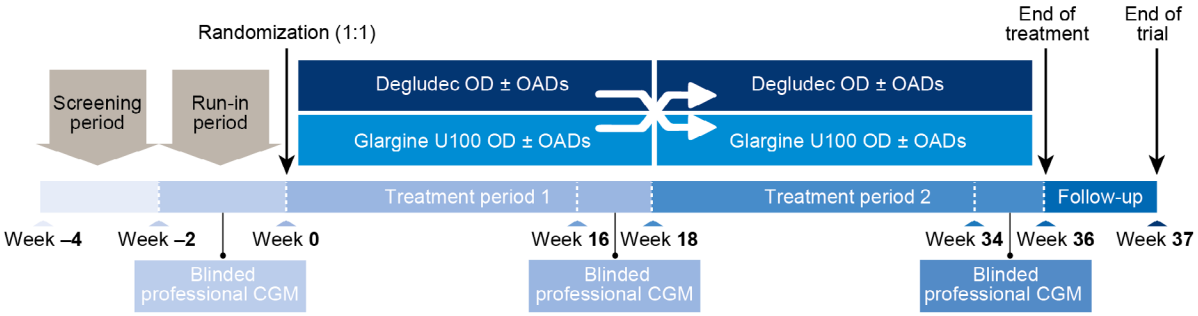

FIGURE 1 Study design. Degludec, insulin degludec 100 U/mL; CGM, continuous glucose monitoring (Abbott FreeStyle Libre Pro); glargine U100, insulin glargine 100 U/mL; OAD, oral antidiabetic drug; OD, once daily

fulfilled at least one of the following criteria for increased risk of hypoglycaemia: one episode of hypoglycaemia (blood glucose <3.9 mmol/L) within 12 weeks prior to screening; at least one severe hypoglycaemic episode within 12 months prior to screening; known hypoglycaemic unawareness; treatment with insulin for >5 years; or moderate renal impairment (estimated glomerular filtration rate [eGFR] 30–59 mL/min/1.73 m^2). Exclusion criteria included: impaired liver function (alanine aminotransferase ≥2.5 times or bilirubin >1.5 times upper normal limit); severe renal impairment (eGFR <30 mL/min/1.73 m^2); and uncontrolled or potentially unstable diabetic retinopathy or maculopathy.

2.3 | Randomization and monitoring

After initial screening, participants undertook a 2-week run-in period to assess adherence to CGM requirements (Figure 1). A criterion for randomization was that subjects were able and willing to adhere to the protocol including requirements and tolerability in regard to wearing the FreeStyle Libre Pro sensor, based on the investigator's opinion. During the study, participants were asked to conduct the CGM periods on days representing their normal daily life, not coinciding with any planned activities that would require assessments to be postponed (e.g. vacations, unusual strenuous exercise, overseas travel), or during local daylight-saving clock shifts or travel across time zones. At the study start (Week 0), eligible participants were randomized 1:1 to either degludec or glargine 100 U/mL glargine U100, each once daily at the same time every day and according to local labels. Participants treated with one or more permitted OADs continued their pre-trial OAD treatment throughout the trial, with no change of dose unless required for safety reasons. Each treatment period consisted of a 16-week titration followed by a 2-week maintenance period, during which participants wore the CGM device. They were then switched to the other trial product (glargine U100 or degludec) for a second treatment period (16-week titration period followed by 2-week maintenance period). Titration was performed once weekly (recommended blood glucose target: 3.9–5.0 mmol/L), with investigator guidance, based on a mean of three pre-breakfast self-measured blood glucose (SMBG) values (performed on 2 days prior to titration, and on the day of each visit, from Week 0 to Week 36 using a blood glucose meter provided by Novo Nordisk). For values in the target range, no adjustment was made. For values of 5.1 to 7.0 mmol/L, the basal insulin dose was increased by 2 units (U) and, for values of 7.1 to 8.0 mmol/L, it was increased by 4 U. Conversely, if one of the SMBG values was in the range 3.1 to 3.8 mmol/L, the basal insulin dose was reduced by 2 U; if it was <3.1 mmol/L, the dose was reduced by 4 U. No maximum insulin dose was specified. Subjects were discontinued from the trial if there was initiation of bolus insulin, GLP-1 receptor agonists, or other diabetes medication(s) for more than 14 continuous days. Intermittent bolus insulin treatment for periods of 14 days or fewer were permitted prior to the day of screening.

Randomization was centralized and used an interactive web response system (IWRS), with simple standard sequential allocation from a blocked randomization schedule (block size of 4) without stratifying factors. The random allocation sequence was generated and imported into the IWRS by Novo Nordisk. Forced randomization was not permitted. All CGM data collected during maintenance periods were blinded to participants and investigators.

The professional CGM system (Abbott FreeStyle Libre Pro; Abbott Diabetes Care, Alameda, California, USA)[20] consisted of a factory-calibrated sensor applied to the back of the subject's upper arm, and a reader (set for date, time and target glucose range) for upload of data to CGM software. The FreeStyle Libre Pro was used as per manufacturer's instructions, with an in-use period of 14 days, after which data were retrieved by study staff through scanning, and glucose levels stored every 15 minutes.[20] CGM readings were blinded to the study participants, as the reader was kept at the study site. The investigator or delegated staff reviewed the CGM data for safety considerations upon download at the site. The protocol did not direct use of CGM values for insulin dose titration. During each CGM measuring period, the device did not alert the participant with alarms for hyper- or hypoglycaemia. The CGM data could be reviewed with study participants after each CGM period. Data for mean time of sensor use at baseline or during the trial were not collected.

2.4 | Outcomes

The primary endpoint, TIR, was the percentage of time spent in the glycaemic range of 3.9 to 10.0 mmol/L, as recommended by the

International Consensus on Time in Range, during the 2-week maintenance periods (weeks 17–18 and 35–36), recorded using CGM and calculated as the number of recorded measurements in range divided by the total number of recorded measurements.[5] Prespecified secondary endpoints included overall and nocturnal percentage of time in tight glycaemic range (which we defined as 3.9–7.8 mmol/L), mean glucose (mmol/L) levels (using CGM) and mean HbA1c levels (mmol/mol and %) during the 2-week maintenance periods.

Prespecified exploratory endpoints included glycaemic variability calculated as the standard deviation (SD; mmol/L) and coefficient of variation (CV;%) of glucose levels, percentage of TBR in the hypoglycaemia alert range (level 1 [L1]: 3.0–3.8 mmol/L)[21] or the clinically significant hypoglycaemic range (level 2 [L2]: <3.0 mmol/L),[21] and the number of overall and nocturnal L2 hypoglycaemic episodes (defined as ≥2 consecutive CGM readings <3.0 mmol/L, separated by 15 minutes above the hypoglycaemic range), all measured by CGM, during the 2-week maintenance periods. Mean daily insulin dose (U) was also measured during the same time periods. CGM was carried out using the Abbott FreeStyle Libre Pro system. The nocturnal period was defined as 00:01 to 05:59 (inclusive). The definitions of glycaemic, hypoglycaemic, hyperglycaemic and nocturnal ranges are shown in Table S1.

Because the safety profiles of degludec and glargine U100 are well characterized, collection of safety data was limited to serious adverse events (SAEs), adverse events (AEs) leading to permanent discontinuation of the trial products, and medication errors related to trial products and pregnancies. *Post hoc* analyses included mean (SD) CGM values at baseline, the risk ratio of achieving a clinically significant ≥5% difference in TIR comparing the two treatments, TAR values (L1 [10.1–13.9 mmol/L] and L2 [>13.9 mmol/L]) during maintenance periods and nocturnal TBR (L1 and L2).[5]

2.5 | Statistical analysis

All prespecified endpoint analyses were performed on a final analysis set comprising participants remaining on assigned treatment and completing ≥70% of 2 weeks' CGM measurements in each maintenance period (as recommended by the International Consensus on Time in Range).[5] The primary endpoint, and most secondary endpoints (overall and nocturnal percentage of time in tight glycaemic range, and mean glucose levels) were analysed with a linear mixed model, with treatment and period as fixed effects, participant as a random effect and with an unstructured residual covariance matrix. Estimated treatment difference (ETD) was calculated as the percentage of TIR, TBR and TAR (*post hoc*) with degludec minus the percentage of TIR, TBR and TAR with glargine U100. One percent was equivalent to 14.4 min/d. For the primary endpoint, multiplicity was accounted for by hierarchical testing, first testing for noninferiority and then superiority. Superiority of degludec compared with glargine U100 in participants was considered confirmed if noninferiority was confirmed and the lower limit of the two-sided 95% confidence interval [CI] of the ETD was above zero, or equivalently, if the *P* value for the one-sided test was less than 2.5%. Secondary endpoints were not corrected for multiplicity.

Mean HbA1c values (for the final analysis set) were analysed with a single two-sided test for statistically significant differences between degludec and glargine U100. Exploratory endpoints relating to TBR, glycaemic variability and mean insulin dose were tested using models similar to the primary endpoint. The number of hypoglycaemic episodes was analysed using negative binomial regression, with treatment and period as fixed effects, subject as a random effect and the log person-years of exposure as an offset. A post hoc analysis was conducted to provide the risk ratio of achieving a clinically significant ≥5% difference in TIR between treatment regimens. An incremental 5% difference in TIR has been associated with clinically significant benefits for people with diabetes, corresponding to a potential ≥0.4% improvement in HbA1c.[6,22] The within-participant difference in TIR between treatments was calculated. This difference allocated participants into one of three numbered groups: (a) ≥5% difference in TIR favouring degludec, (b) ≥5% difference in TIR favouring glargine U100 and (c) <5% difference in TIR between the two treatments. The risk ratio was the proportion in group one divided by the proportion in group two. A sensitivity analysis was performed to account for heteroscedasticity, due to a varying number of CGM readings completed, and to look at the impact of concomitant ascorbic acid or salicylic acid.[23] Specifically, the primary endpoint, and selected secondary and exploratory endpoints, were analysed by applying the weight statement in the proc mixed procedure with weights calculated as the square root of the total number of CGM readings. The accuracy of CGM measurements with the FreeStyle Libre Pro can be influenced by intake of ascorbic and/or salicylic acid. Up to 1000 mg of ascorbic acid and up to 650 mg of salicylic acid, daily, are acceptable to avoid interference.[24] A sensitivity analysis was also performed to look at the impact of concomitant ascorbic acid and/or salicylic acid where all CGM measurements, for subjects in the per protocol analysis set, coinciding with intake of these compounds were excluded. Weighting was applied as described previously to account for heteroscedasticity due to a varying number of CGM readings.

Sample size determination, based on the primary endpoint, was performed using the paired *t*-test and was influenced by results from a previous Novo Nordisk trial with a similar design (NCT01569841; NN1250-3874). To detect a mean difference of 0.39 hours with 85% power and with an SD of 2.6, based on a paired *t*-test and 1:1 randomization, required 401 participants to be included in the per-protocol population.

3 | RESULTS

The CONSORT flow diagram for study participants is presented in Figure 2. Of the 613 participants screened, 498 (representing the full analysis set) were randomized to receive treatment (degludec/glargine U100 [n = 249] or glargine U100/degludec [n = 249]). A total of 22 participants withdrew from the study during the first treatment period and eight withdrew in the second period. An additional 20 participants

completed the trial but were excluded from the final analysis because of insufficient CGM data, so 448 participants were included in the final analysis set. The cause of insufficient CGM data in these 20 participants was mainly attributable to technical issues. Baseline characteristics were similar between the two treatment-sequence arms (Table 1). The mean (SD) age was similar between treatment sequences (62.9 [10.0] and 62.7 [9.7] years for degludec/glargine U100 and glargine U100/degludec, respectively). This was also the case for mean [SD] duration of diabetes (14.5 [7.0] and 15.6 [8.3] years), HbA1c (59.6 [10.9] mmol/mol, or 7.6 [1.0]%, and 59.6 [10.9] mmol/mol, or 7.6 [1.0]%) and baseline CGM-measured blood glucose levels (8.6 [2.5] and 8.5 [2.3] mmol/L; Table 1).

3.1 | Primary endpoint

Noninferiority and superiority were confirmed for degludec versus glargine U100 for the primary endpoint, with significantly more TIR (3.9–10.0 L/L) with degludec compared with glargine U100 (mean 72.1% vs. 70.7%, respectively; ETD 1.43% [95% CI: 0.12, 2.74; $P = 0.032$]). This was equivalent to an additional 20.6 minutes of TIR per day with degludec versus glargine U100 (Table 2). Significantly more participants also achieved a clinically significant ≥5% difference in TIR with degludec (39.5%) than with glargine U100 (28.8%; risk ratio 1.37 [95% CI: 1.09, 1.72]; *post hoc*).

3.2 | Secondary endpoints

Overall time spent in tight glycaemic range (3.9–7.8 mmol/L) was significantly greater with degludec versus glargine U100, with an ETD of 1.52% (95% CI: 0.15, 2.89), equating to 21.9 additional minutes per day. Nocturnal time spent in tight glycaemic target range (Table 2) and mean CGM-measured glucose levels were similar between groups (7.6 mmol/L for degludec, 7.6 mmol/L for glargine U100; ETD 0.0 mmol/L (95% CI: −0.2, 0.1]). Mean HbA1c values were numerically similar for degludec (54.1 mmol/mol [7.1%]) and glargine U100 (54.8 mmol/mol [7.2%]) but the treatment difference reached statistical significance (ETD −0.06% [95% CI: −0.11, −0.01]). A graphical plot of mean HbA1c values by treatment week is presented in Figure S1.

3.3 | Exploratory endpoints

Glycaemic variability was similar between degludec and glargine U100. The estimated SD of CGM glucose levels was 2.6 mmol/L for degludec and 2.7 mmol/L for glargine U100 (ETD 0.0 mmol/L [95% CI: −0.1, 0]), with a CV of 34.5% for degludec versus 34.9% for glargine U100 (ETD −0.47% [95% CI: −0.99, 0.06]). The mean daily basal insulin dose was significantly lower for participants receiving degludec compared with glargine U100 (56.3 U and 58.6 U, respectively; ETD −2.25 U [95% CI: −3.47, −1.03]; Figure S2).

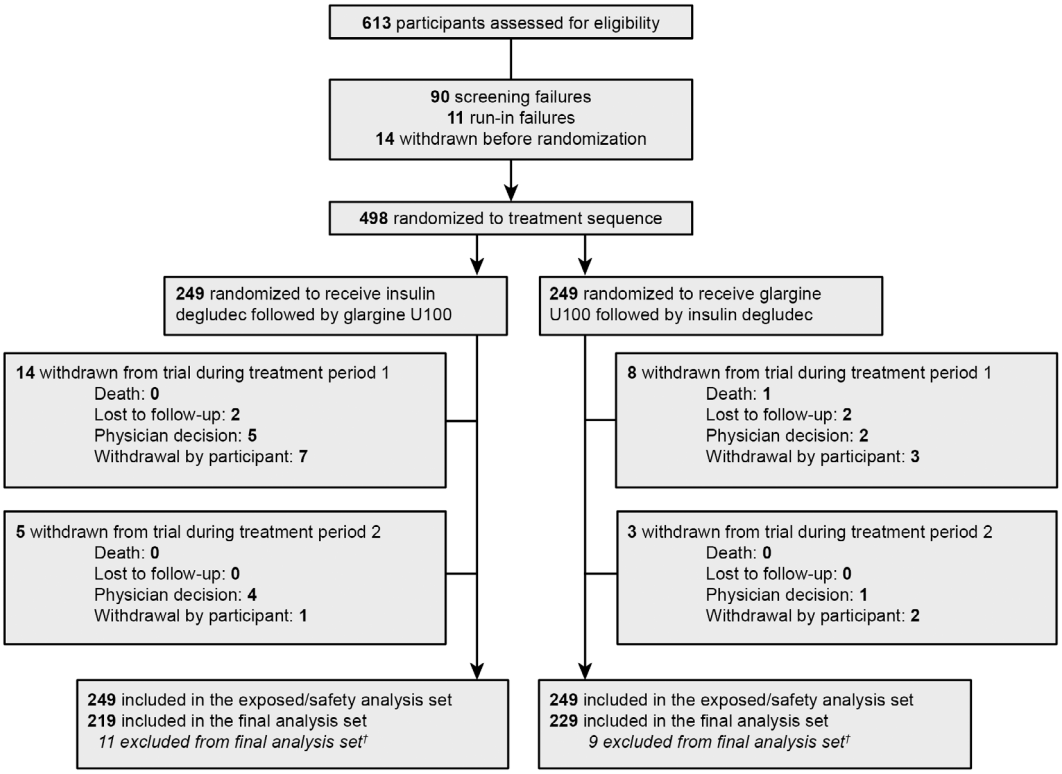

FIGURE 2 CONSORT flow diagram for the SWITCH PRO trial (NCT03687827). †20 participants were excluded from the final analysis set due to insufficient CGM data. Final analysis set: participants who completed the trial with full CGM assessments equaling a minimum of 10 days' CGM data per maintenance period. CGM, continuous glucose monitoring; glargine U100, insulin glargine 100 U/mL

TABLE 1 Baseline demographics and characteristics

	Degludec/glargine U100 (n = 249)	Glargine U100/degludec (n = 249)
Age, years	62.9 (10.0)	62.7 (9.7)
Duration of diabetes, years	14.5 (7.0)	15.6 (8.3)
BMI, kg/m^2	32.4 (5.5)	32.1 (5.3)
HbA1c mmol/mol %	59.6 (10.9) (7.6 [1.0])	59.6 (10.9) (7.6 [1.0])
Male, %	47.4	48.6
Patients taking OADs, n (%)	221 (88.8)	224 (90.0)
Number of OADs at screening, n (%)		
0	28 (11.2)	25 (10.0)
1	137 (55.0)	141 (56.6)
≥2	84 (33.7)	83 (33.3)
Insulin type at screening, n (%)[a]		
Basal	204 (81.9)	207 (83.1)
Glargine U100	131 (52.6)	129 (51.8)
Glargine U300	27 (10.8)	30 (12.0)
Degludec	26 (10.4)	28 (11.2)
Insulin detemir	20 (8.0)	20 (8.0)
Intermediate-acting insulin		
NPH	39 (15.7)	41 (16.5)
Human insulin	2 (0.8)	0 (0)
CGM[b]		
Mean glucose levels, mmol/L (SD)	8.6 (2.5)	8.5 (2.3)
TIR (3.9–10.0 mmol/L) (%)	65.5 (21.8)	65.0 (21.3)
TBR (L1: 3.0–3.8 mmol/L) (%)	3.8 (5.1)	4.0 (6.1)
TBR (L2: <3.0 mmol/L) (%)	1.7 (4.0)	1.8 (4.2)
TAR (L1: 10.1–13.9 mmol/L) (%)	20.0 (13.6)	20.7 (14.2)
TAR (L2: >13.9 mmol/L) (%)	9.0 (15.2)	8.5 (12.8)

Note: Full analysis set. Data are mean (SD) unless otherwise stated; baseline refers to Week 0 (randomization) except for age, which was recorded at screening.
Abbreviations: BMI, body mass index; CGM, continuous glucose monitoring; degludec, insulin degludec 100 U/mL; glargine U100, insulin glargine 100 U/mL; L, level; NPH, neutral protamine Hagedorn; OAD, oral antidiabetic drug; SD, standard deviation; T1, treatment period 1; T2, treatment period 2; TAR, time above range; TBR, time below range; TIR, time in range.
[a]Basal: degludec, glargine U100, glargine U300, insulin detemir; bolus: human insulin.
[b]Baseline CGM-measured glucose levels were taken during weeks −2 to 0 (run-in to randomization).

Overall time spent in the hypoglycaemia alert range (L1: 3.0–3.8 mmol/L) was similar between degludec and glargine U100 (ETD −0.47% [95% CI: −1.07; 0.14]; Table 2). Overall time spent in the clinically significant hypoglycaemic range (L2: <3.0 mmol/L) was similar for degludec compared with glargine U100 (L2: ETD −0.24% [95% CI: −0.79, 0.31]; Table 2). However, nocturnal TBR was significantly lower with degludec versus glargine U100 (ETD for L1: −0.59% [−8.5 min/d; 95% CI: −0.89, −0.29]; ETD for L2: −0.29% [−4.2 min/d; 95% CI: −0.54, −0.04]; ETD for L1 + L2: −0.88% [−12.7 min/d; 95% CI: −1.34, −0.42]; *post hoc* [Table 2]).

Numerically fewer overall hypoglycaemic L2 episodes were observed with degludec compared with glargine U100 (treatment rate ratio 0.87 [95% CI: 0.75, 1.00]), and significantly fewer nocturnal hypoglycaemic L2 episodes were observed with degludec compared with glargine U100 (31.1 versus 40.9 patient-years of exposure; estimated rate ratio 0.76 [95% CI: 0.65, 0.90]; Table S2).

Further post hoc analysis demonstrated that L1 TAR (10.1–13.9 mmol/L) was 15.2% for degludec and 15.8% for glargine U100 (ETD −0.59% [−8.6 min/d]; 95% CI: −1.50, 0.31), and L2 TAR (>13.9 mmol/L) was 4.7% for degludec and 4.8% for glargine U100 (ETD −0.13% [−1.9 min/d]; 95% CI: −0.86, 0.59; Table 2).

3.4 | Sensitivity analyses

Results from sensitivity analyses demonstrated that the primary analysis was not influenced by concomitant use of ascorbic or salicylic acid, or variability in the number of CGM readings (Figure S3). Results from

TABLE 2 Treatment difference between degludec and glargine U100 for time in glycaemic, hypoglycaemic and hyperglycaemic range

		Degludec (n = 448)	Glargine U100 (n = 448)	ETD (degludec−glargine U100)		
		Estimated mean (%)		%	95% CI	Min/d[b]
Primary endpoint						
TIR (3.9–10.0 mmol/L)		72.1	70.7	1.43	[0.12, 2.74]; (P = 0.032)	20.6
Secondary endpoints						
Tight TIR (3.9–7.8 mmol/L)	Overall	53.0	51.5	1.52	[0.15, 2.89]	21.9
	Nocturnal	15.2	14.9	0.24	[−0.25, 0.74]	3.5
Exploratory endpoints						
TBR (L1: 3.0–3.8 mmol/L)	Overall	5.8	6.3	−0.47	[−1.07, 0.14]	−6.8
	Nocturnal[a]	2.4	3.0	−0.59	[−0.89, −0.29]	−8.5
TBR (L2: <3.0 mmol/L)	Overall	2.2	2.5	−0.24	[−0.79, 0.31]	−3.5
	Nocturnal[a]	1.0	1.3	−0.29	[−0.54, −0.04]	−4.2
TBR (L1 + 2: ≤3.8 mmol/L)	Overall	8.1	8.8	−0.71	[−1.68, 0.26]	−10.2
	Nocturnal[a]	3.4	4.3	−0.88	[−1.34, −0.42]	−12.7
TAR (L1: 10.1–13.9 mmol/L)	Overall[a]	15.2	15.8	−0.59	[−1.50, 0.31]	−8.6
TAR (L2: >13.9 mmol/L)	Overall[a]	4.7	4.8	−0.13	[−0.86, 0.59]	−1.9

Note: Final analysis set. Endpoints are prespecified unless otherwise noted. Secondary and exploratory endpoints regarding time spent in target range are analyzed and tested using the same model as the primary endpoint.

Abbreviations: degludec, insulin degludec 100 U/mL; ETD, estimated treatment difference; glargine U100, insulin glargine 100 U/mL; L1, level 1 hypoglycaemia alert range; L2, level 2 clinically significant hypoglycaemia alert range; TAR, time above range; TBR, time below range; TIR, time in range.

[a]*Post hoc* analysis.

[b]1% translates to 14.4 min.

the sensitivity analyses of secondary and exploratory analyses were in agreement with the reported endpoints.

3.5 | Adverse events

A summary of treatment-emergent SAEs (in all randomized participants) is provided in Table S3. The frequency of SAEs was similar with degludec (36 events) and glargine U100 (35 events), and one event in each treatment arm was related to hypoglycaemia. One fatality was reported during the trial and was determined as unlikely to be related to treatment. No new safety issues related to degludec were identified.

4 | DISCUSSION

In this randomized, head-to-head study in basal insulin-treated adults with type 2 diabetes and at least one risk factor for hypoglycaemia, the use of CGM showed that a treatment period with degludec was associated with significantly more TIR (3.9–10.0 mmol/L) compared with glargine U100, with an additional 20.6 minutes of TIR per day on average.

CGM also showed that participants spent more time in tight glycaemic target range, had less nocturnal TBR and experienced fewer episodes of nocturnal hypoglycaemia during treatment with degludec compared with glargine U100. While an overall reduction of 0.7% in TBR was observed with degludec, there was also a nonsignificant 0.7% reduction in TAR (Table 2), suggesting that reduced hyperglycaemic excursions (as well as reduced time in low blood glucose) contribute to the increased TIR.

In addition, more individual participants achieved a clinically significant ≥5% difference in TIR during treatment with degludec than with glargine U100. This outcome was chosen because previous data suggest that each incremental 5% difference in TIR is associated with clinically significant benefits for people with diabetes, corresponding to a potential ≥0.4% improvement in HbA1c.[6,22] In the present study, the ETD in HbA1c was −0.06% in favour of degludec. Although statistically significant, this difference is below the threshold considered to be of clinical significance. The patient population in this study was relatively well controlled at baseline on a combination of basal insulin and OADs. It is possible that the differences seen in CGM findings with degludec versus glargine U100 may have been more pronounced in a population that was more insulin-deficient, or that had greater incidence of baseline hypoglycaemia or glycaemic variability. In addition, as the CGM data were allowed to be shared with the subject by the investigators and study staff after each CGM period, it is possible that awareness of glucose patterns may have influenced subsequent titration decisions, which could potentially have decreased potential differences in the treatments. More research is needed to understand how differences in CGM metrics will be predictive of outcomes.

The combination of (a) a significantly lower nocturnal TBR with degludec versus glargine U100, captured with blinded CGM, together with (b) significantly fewer nocturnal hypoglycaemic episodes is in agreement with the decreased incidence of hypoglycaemia with degludec seen in previous trials, including SWITCH 2.[11-13,16] SWITCH PRO had the same inclusion and exclusion criteria as the SWITCH 2 trial, and the data presented here for SWITCH PRO show a CGM-detected hypoglycaemia rate ratio for degludec versus glargine U100 of 0.87 (95% CI: 0.75, 1.00). In contrast, during the SWITCH 2 trial, which reported severe or blood-glucose-confirmed symptomatic hypoglycaemic episodes during the 16-week maintenance phase, the degludec versus glargine U100 hypoglycaemia rate ratio was 0.70 (95% CI: 0.61, 0.80).[16] A *post hoc* analysis of SWITCH 2[25] extended the analysis to include asymptomatic as well as symptomatic events, an outcome that may be considered more similar to the present CGM-derived definition of hypoglycaemic events. It reported an overall hypoglycaemia (symptomatic or asymptomatic) rate ratio of 0.76 (95% CI: 0.67, 0.85). The difference in hypoglycaemia rate ratios between SWITCH PRO and SWITCH 2 could be explained by the use of CGM to capture hypoglycaemia, the difference in hypoglycaemia definitions between trials, and the fact that SWITCH 2 had 32-week treatment periods, meaning that data were collected over longer time intervals than in our 2-week maintenance periods.

CGM could provide an opportunity to capture asymptomatic and nocturnal episodes of hypoglycaemia, and help provide insight into nocturnal glycaemic patterns.[26-28] CGM, compared with conventional monitoring such as SMBG testing, has previously shown a tendency toward reporting lower mean glucose concentrations[29] or an increased prevalence of unrecognized hypoglycaemic episodes,[16,30,31] and studies have suggested that many hypoglycaemic episodes are asymptomatic and go unnoticed without the use of CGM.[32] CGM had not been tested thoroughly enough at the time of the design of this trial, but its use should be considered for future studies. Its use in SWITCH PRO could potentially have resulted in the capture of more hypoglycaemic episodes.

As this was a crossover trial, there was a potential risk of carryover effects between treatment periods. However, the use of 16-week titration periods minimized this risk, and data capture for the main endpoints was limited to the two 2-week maintenance periods during which participants had their basal insulin titrated to comparable fasting target levels. Mean pre-breakfast SMBG was 5.5 versus 5.6 mmol/L with degludec versus glargine U100 at Week 18, and 5.4 versus 5.5 mmol/L at Week 36. The very similar estimated HbA1c values support this.

A strength of the present study was that CGM allowed more comprehensive capture of the frequency of hypoglycaemic events (especially at night) compared with conventional methods such as SMBG. More nocturnal hypoglycaemic events were therefore reported that would otherwise have remained undetected. In addition, the crossover design meant that participants were compared with themselves, acting as internal controls, thus ensuring homogeneity in baseline characteristics and treatment adherence. It also enabled a reduced cohort size to be used, which has practical value when studying technologies such as CGM, which require participant training and outlay.

In conclusion, this was the first head-to-head study using CGM to measure glycaemic TIR as the primary outcome with two widely used basal insulin analogues, in basal insulin-treated people with type 2 diabetes and at least one hypoglycaemia risk factor. In this study, treatment with degludec, compared with glargine U100, was shown by CGM to result in more time in glycaemic range and less nocturnal TBR. These observations may help explain the lower incidence of hypoglycaemic events despite equivalent HbA1c reported in previous trials of these comparators.

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CONFLICT OF INTEREST

R.G. has received research support from Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Janssen, Medtronic, Merck, Novartis, Novo Nordisk, Roche, Sanofi and Takeda, has served on advisory panels for AstraZeneca, Boehringer Ingelheim, Eli Lilly, HLS Therapeutics, Janssen, Merck, Novo Nordisk, Roche, Sanofi and Takeda, and on speaker bureaus for Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, HLS Therapeutics, Janssen, Merck, Novo Nordisk, Sanofi and Servier, and reports consulting for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Novo Nordisk and Takeda. V.R.A. has received research support from AstraZeneca/BMS, Boehringer Ingelheim, Calibra, Eisai, Fractyl, Janssen, Novo Nordisk, Sanofi and Theracos, and has served as a consultant for Adocia, Applied Therapeutics, AstraZeneca, Becton Dickinson, Duke, Medscape, IMNE, Liberum, Novo Nordisk, Sanofi, Tufts and Zafgen; V.R.A.'s spouse has been an employee of Merck and Janssen, receiving employee benefits. L.K.B. has received consultancy fees from Novo Nordisk, Sanofi and Eli Lilly. A.S.L.C. is an employee of Novo Nordisk and holds shares. A.MD. and E.PR. are employees of Novo Nordisk. G.P. has served on a scientific advisory board for Eli Lilly. K.R. has received financial support from Sanofi, Amgen, Novo Nordisk and Mylan for consultancy, board membership, honoraria and travel fees; and also reports grant support from Sanofi for her institution. D.C.K. is a consultant to Eoflow, Fractyl, Lifecare, Novo Nordisk, Roche Diagnostics, Samsung and Thirdwayv. R.M.B. has received research support from, consulted for or has been on a scientific

advisory board for Abbott Diabetes Care, Ascensia, Dexcom, Eli Lilly, Hygieia, Johnson & Johnson, Medtronic, Novo Nordisk, Onduo, Roche, Sanofi and United Healthcare. R.M.B.'s employer, nonprofit HealthPartners Institute, contracts for his services, and no personal income goes to him.

AUTHOR CONTRIBUTIONS

Ronald M. Goldenberg is the guarantor of this work and, as such, had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors confirm that they meet the International Committee of Medical Journal Editors (ICJME) uniform requirements for authorship and that they have contributed to the roles detailed below. Ronald M. Goldenberg and Richard M. Bergenstal made substantial contributions to conception or design of the work, and Ronald M. Goldenberg, Ehsan Parvaresh Rizi, Sia Louise Christiansen, Anders Meller Donatsky and Richard M. Bergenstal contributed to the acquisition, analysis or interpretation of data for the work. All authors were involved in the drafting and critical revision of the work for important intellectual content, and all approved the final version to be published.

DATA-SHARING STATEMENT

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

PRIOR PRESENTATION

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PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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