Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial

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Summary

Background Basal insulin therapy does not stop loss of β-cell function, which is the hallmark of type 2 diabetes mellitus, and thus diabetes control inevitably deteriorates. Insulin degludec is a new, ultra-longacting basal insulin. We aimed to assess efficacy and safety of insulin degludec compared with insulin glargine in patients with type 2 diabetes mellitus.

Methods In this 52 week, phase 3, open-label, treat-to-target, non-inferiority trial, undertaken at 123 sites in 12 countries, we enrolled adults (aged ≥18 years) with type 2 diabetes mellitus and a glycated haemoglobin (HbA_{1c}) of 7·0–10·0% after 3 months or more of any insulin regimen (with or without oral antidiabetic drugs). We randomly allocated eligible participants in a 3:1 ratio to receive once-daily subcutaneous insulin degludec or glargine, stratified by previous insulin regimen, via a central interactive response system. Basal insulin was titrated to a target plasma glucose concentration of 3·9–<5·0 mmol/L self-measured before breakfast. The primary outcome was non-inferiority of degludec to glargine measured by change in HbA_{1c} from baseline to week 52 (non-inferiority limit of 0·4%) by ANOVA in the full analysis set. We assessed rates of hypoglycaemia in all treated patients. This study is registered with ClinicalTrials.gov, number NCT00972283.

Findings 744 (99%) of 755 participants randomly allocated degludec and 248 (99%) of 251 allocated glargine were included in the full analysis set (mean age 58·9 years [SD 9·3], diabetes duration 13·5 years [7·3], HbA_{1c} 8·3% [0·8], and fasting plasma glucose 9·2 mmol/L [3·1]); 618 (82%) and 211 (84%) participants completed the trial. After 1 year, HbA_{1c} decreased by 1·1% in the degludec group and 1·2% in the glargine group (estimated treatment difference [degludec–glargine] 0·08%, 95% CI –0·05 to 0·21), confirming non-inferiority. Rates of overall confirmed hypoglycaemia (plasma glucose <3·1 mmol/L or severe episodes requiring assistance) were lower with degludec than glargine (11·1 *vs* 13·6 episodes per patient-year of exposure; estimated rate ratio 0·82, 95% CI 0·69 to 0·99; p=0·0359), as were rates of nocturnal confirmed hypoglycaemia (1·4 *vs* 1·8 episodes per patient-year of exposure; 0·75, 0·58 to 0·99; p=0·0399). Rates of severe hypoglycaemia seemed similar (0·06 *vs* 0·05 episodes per patient-year of exposure for degludec and glargine) but were too low for assessment of differences. Rates of other adverse events did not differ between groups.

Interpretation A policy of suboptimum diabetes control to reduce the risk of hypoglycaemia and its consequences in advanced type 2 diabetes mellitus might be unwarranted with newer basal insulins such as degludec, which are associated with lower risks of hypoglycaemia than insulin glargine.

Funding Novo Nordisk.

Introduction

The landmark UK Prospective Diabetes Study (UKPDS)[1] showed that, because of unremitting loss of β-cell function that characterises type 2 diabetes mellitus, a substantial number of patients need insulin therapy after 9 years or more of disease. Moreover, many patients need intensification to a basal-bolus insulin regimen after 3–5 years of basal insulin treatment.[1] Hypoglycaemia is the main restricting factor in glycaemic management of type 2 diabetes mellitus, leading to physical and psychosocial morbidity and perhaps even mortality.[2] Variability in absorption and duration of action and time-action profile peaks associated with administration of subcutaneous insulin can contribute to hypoglycaemia. Therefore, we need an effective basal insulin with a long, flat, and stable profile, and a lowered risk of hypoglycaemia.

Insulin degludec is an ultra-longacting basal insulin in clinical development for the treatment of diabetes. Insulin degludec forms soluble multihexamers on subcutaneous injection, resulting in a depot from which

monomers are slowly and continuously absorbed into the circulation. This mechanism leads to the reported ultra-long pharmacokinetic and pharmacodynamic profiles and reduced variability in insulin action compared with insulin glargine.[3–5] A previous proof-of-concept phase 2 clinical trial[6] comparing once-daily insulin degludec with insulin glargine in patients with type 2 diabetes mellitus not previously treated with insulin showed similar efficacy and suggested lower rates of hypoglycaemia with insulin degludec. In this phase 3, BEGIN Basal-bolus Type 2 study, we aimed to assess the efficacy and safety of insulin degludec compared with insulin glargine in a basal-bolus regimen in patients with longstanding type 2 diabetes mellitus.

Methods

Trial design and participants

In our phase 3, 52-week, randomised, treat-to-target, parallel-group, open-label, non-inferiority trial, we compared the efficacy and safety of once-daily insulin degludec with once-daily insulin glargine in a basal-bolus regimen with mealtime insulin aspart, with or without metformin, pioglitazone, or both in participants with type 2 diabetes mellitus. We undertook the trial at 123 sites in 12 countries (Bulgaria, Germany, Hong Kong, Ireland, Italy, Romania, Russia, Slovakia, South Africa, Spain, Turkey, and the USA).

Adults (aged ≥18 years) who had had type 2 diabetes mellitus for at least 6 months, and had glycated haemoglobin (HbA_{1c}) concentrations of 7·0–10·0% (53–86 mmol/mol; inclusive), and a body-mass index of 40·0 kg/m² or less, who had been treated with any insulin regimen for at least 3 months with or without oral antidiabetic drugs before screening were eligible for inclusion. Patients were excluded if they had taken glucagon-like peptide-1 receptor agonists or rosiglitazone within the previous 3 months (see appendix for a full list of inclusion and exclusion criteria).

The protocol was approved by independent ethics committees or institutional review boards before the start of the trial and written informed consent was obtained from participants before enrolment. The trial was undertaken in accordance with the Declaration of Helsinki and the International Conference on Harmonisation good clinical practice guidelines.[7,8]

Randomisation and masking

Eligible participants were randomly assigned in a 3:1 ratio through a central interactive voice response or web response system to receive once-daily subcutaneous insulin degludec (100 U/mL, 3 mL FlexPen, Novo Nordisk, Bagsvaerd, Denmark) or once-daily subcutaneous insulin glargine (Lantus, 100 U/mL, 3 mL SoloStar, Sanofi-Aventis, Paris, France), both in combination with subcutaneous meal-time insulin aspart (100 U/mL, NovoRapid/NovoLog, 3 mL FlexPen, Novo Nordisk), with or without previously prescribed metformin, pioglitazone, or both.

Participants were stratified at randomisation by previous insulin regimen at screening (basal only *vs* basal-bolus or pump *vs* other). We used an open-label design because the pen devices used to administer the basal insulins differed in appearance and a double-dummy design was not possible because no placebo pen devices are available. The safety committee from the sponsor (Novo Nordisk) that undertook safety surveillance, the titration committee (Novo Nordisk) and the external cardiovascular event adjudication committee were masked to treatment-group assignment. All Novo Nordisk staff involved in data handling were masked to participants' treatment allocation until the dataset was locked for statistical analysis.

Procedures

Participants discontinued all oral antidiabetic drugs apart from metformin or pioglitazone at randomisation (week 0). No additional antidiabetic treatments were allowed during the trial and the regimens of metformin and pioglitazone (including dose and dosing frequency) were maintained.

Eligible participants received insulin degludec once-daily at the main evening meal or, in accordance with its product labelling, insulin glargine once-daily at any time during the day (but at the same time each day) at the investigator's discretion. Participants received insulin aspart at breakfast, lunch, and dinner and subsequent dosing was allowed with a fourth meal.

Basal insulins were systematically titrated with a treat-to-target approach to a self-measured plasma glucose concentration (SMPG) before breakfast of 3·9–<5·0 mmol/L (see appendix for details). On the basis of the average of three consecutive before-breakfast SMPG values before every visit and the last dose of basal insulin, a new dose was proposed via an electronic data capture system to the investigator, who could accept or reject this dose. Investigators based their decisions on the average before-breakfast SMPG and other available data (eg, additional plasma glucose measurements, hypoglycaemic episodes, or known lifestyle changes). The masked titration committee reviewed and, if necessary, addressed all deviations from the proposed dose, and queried investigators with frequent email communications. Bolus insulin was to be titrated after the basal insulin was titrated.

See Online for appendix

The primary endpoint was change from baseline in HbA_{1c} concentration after 52 weeks of treatment. Secondary efficacy endpoints included change from baseline in central laboratory-measured fasting plasma glucose, mean SMPG (appendix), prandial plasma glucose increment, time to reach the SMPG target before breakfast of 3·9–<5·0 mmol/L from 4-point and 9-point SMPG profiles, and health-related quality of life (HRQoL). Safety assessments included adverse events, hypoglycaemic episodes, insulin dose, physical examination, bodyweight, vital signs, fundoscopy,

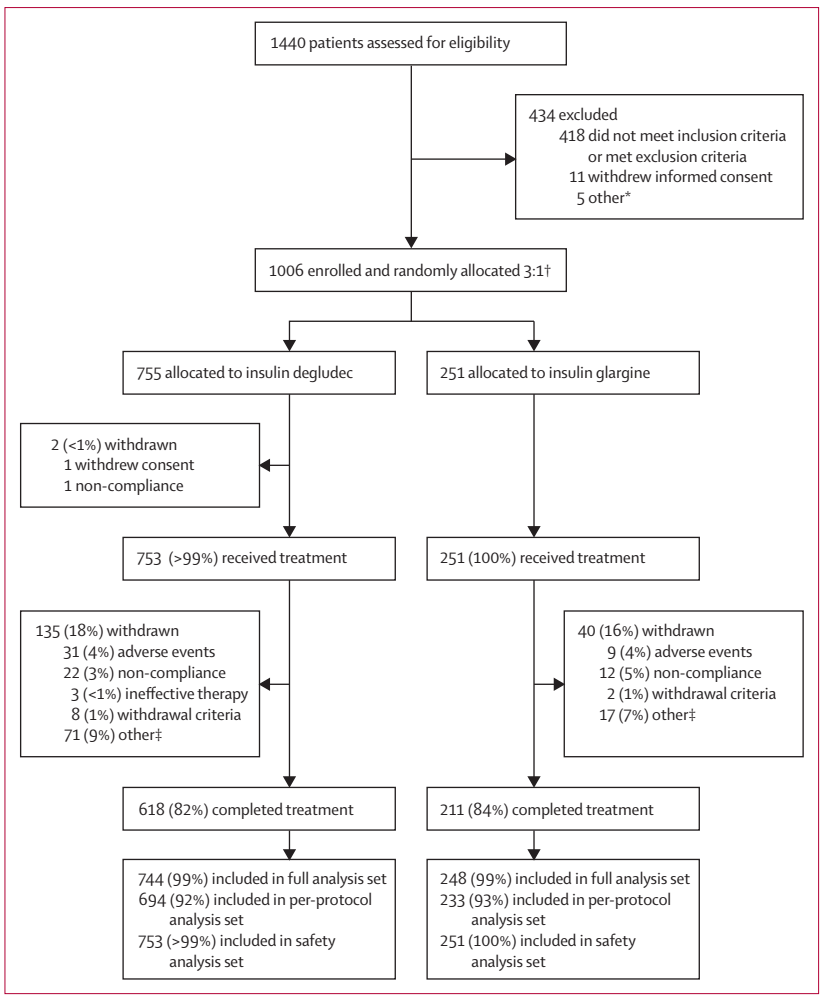

Figure 1: **Trial profile**
The full analysis set consisted of all participants who were randomly assigned treatment excluding patients (n=14) from one closed trial site. The safety analysis set consisted of all participants who received at least one dose of study drug. The per-protocol analysis set consisted of participants with exposure to treatment for at least 12 weeks who did not have any major protocol violations that could affect the primary endpoint and had a valid glycated haemoglobin (HbA_{1c}) assessment at baseline and at (or after) 12 weeks. *For two participants, laboratory results were not available at randomisation visit; another two participants visited outside the randomisation period; an error occurred in number assignment for one participant. †14 randomly allocated patients (11 in the insulin degludec and three in the insulin glargine group) from one closed trial site were excluded from the full analysis set before the trial was unmasked. ‡For other reasons see appendix.

electrocardiogram (ECG), and laboratory tests. Confirmed hypoglycaemia was defined as those episodes in which the plasma glucose value was lower than 3·1 mmol/L (irrespective of symptoms) or severe (requiring assistance).[9] Hypoglycaemic episodes occurring between 0001 h and 0559 h (inclusive) were classified as nocturnal, and those occurring between 0600 h and 0000 h (inclusive) as diurnal. The independent event adjudication committee assessed cardiovascular events.

Laboratory analyses were undertaken at Quintiles Central Laboratories in the UK, Singapore, South Africa, and the USA. We used validated short form (SF)-36 questionnaires to assess HRQoL outcomes (appendix).[10]

Statistical analysis

Our trial's primary objective was to confirm the non-inferiority of insulin degludec to insulin glargine as assessed by change in HbA_{1c} concentration from baseline after 52 weeks, with a non-inferiority limit of 0·4% for the treatment difference.[11] We calculated the sample size on the basis of this primary objective with a *t* statistic under the assumption of a one-sided test of size 2·5% and a zero mean treatment difference and standard deviation estimate of 1·3% for HbA_{1c} concentration (appendix).

Participants in the full analysis set (all participants randomly allocated to treatment apart from those from one closed trial site who were excluded before unmasking of treatment groups) were included in the statistical assessments of all efficacy endpoints and treatment comparisons of hypoglycaemia, bodyweight, and lipids. We assessed other safety endpoints in participants exposed to treatment (safety analysis set). We imputed missing values by the last observation carried forward approach. Treatment difference in changes in HbA_{1c} concentration from baseline after 52 weeks were assessed by use of an ANOVA model, with treatment, antidiabetic therapy at screening, sex, and region as fixed factors, and age and baseline value as covariates. Non-inferiority was confirmed if the upper limit of the 95% CI for the treatment difference was 0·4% (4·4 mmol/mol) or less. Details of the additional sensitivity analyses of the primary endpoint (per-protocol population, all randomised participants, simple model with only baseline HbA_{1c} concentration as covariate, and a repeated measurement model) are provided in the appendix.

We analysed treatment difference as change from baseline in fasting plasma glucose concentration, bodyweight, prandial increments, mean plasma glucose (based on the 9-point SMPG profile), and HRQoL by use of an ANOVA method akin to that used for the primary endpoint. We analysed the number of treatment-emergent confirmed hypoglycaemic episodes per patient-year exposure with a negative binomial regression model including treatment, antidiabetic therapy at screening, sex, and region as fixed factors, and age as covariate for all reported treatment-emergent episodes (predefined analysis). The same model was used for a post-hoc analysis of treatment-emergent confirmed hypoglycaemic episodes occurring from week 16 to week 52 after basal insulin dose and glycaemic control stabilised (ie, maintenance period). We controlled for type 1 error by adopting a hierarchical (fixed-sequence) testing procedure for selected endpoints, including change in HbA_{1c} concentration, number of confirmed hypoglycaemic episodes, and change in fasting plasma glucose concentrations (appendix).

Role of the funding source

The sponsor contributed to the trial design, data collection, statistical analyses, and the preparation of the clinical study report. All authors had full access

to data and shared final responsibility for the content of the manuscript and the decision to submit for publication.

Results

We enrolled and assessed participants between Sept 1, 2009, and Oct 28, 2010. 618 (82%) of 755 participants randomly assigned insulin degludec and 211 (84%) of 251 randomly assigned insulin glargine completed the trial (figure 1). The proportion of participants who withdrew and reasons for withdrawal were similar in the two groups (figure 1).

Demographic and baseline characteristics were very similar between groups and were representative of a population with type 2 diabetes mellitus requiring basal-bolus insulin therapy (table 1). At screening in the full analysis set, 321 (43%) of 744 participants in the insulin degludec group and 103 (42%) of 248 participants in the insulin glargine group had previously used insulin glargine, compared with 112 (15%) of 744 and 48 (19%) of 248 who had used insulin detemir and 221 (30%) of 744 and 65 (26%) of 248 who had used insulin aspart.

At 52 weeks, mean HbA_{1c} concentration had decreased in both treatment groups (figure 2, appendix). The estimated mean change from baseline was –1·10% with insulin degludec and –1·18% with insulin glargine; the estimated treatment difference of 0·08% (95% CI –0·05 to 0·21) confirmed the non-inferiority of insulin degludec to insulin glargine. All supportive analyses showed non-inferiority between treatments (appendix): analysis of the per-protocol population (estimated mean change from baseline of –1·18% with insulin degludec and –1·22% with insulin glargine; estimated treatment difference 0·05% [–0·08 to 0·18]), analysis of all randomised participants, analysis with a simple model containing only baseline HbA_{1c} concentration as a covariate, and analysis with a repeated measurement model. The proportion of participants who achieved the HbA_{1c} target of less than 7% (53 mmol/mol) at week 52 was 368 (49%) of 744 with insulin degludec and 124 (50%) of 248 with insulin glargine. Concentrations of fasting plasma glucose decreased by 2·3 mmol/L with insulin degludec and 2·0 mmol/L with insulin glargine (estimated treatment difference –0·29 mmol/L [–0·65 to 0·06]; p=0·1075; figure 2, appendix). 9-point SMPG profiles seemed similar for the two treatment groups at baseline and decreased in both groups by week 52 (figure 2). After 52 weeks, mean prandial increments were similar between treatment groups for all meals (ie, breakfast, lunch, and main evening meal); the mean mealtime increment was 1·3 mmol/L for both groups.

Mean insulin doses did not differ between the groups at baseline (table 2) and increased throughout the trial—most rapidly during the first 16 weeks—for both basal and bolus insulin (appendix). At 52 weeks, the split between basal and bolus doses showed more basal insulin used in the insulin degludec group and slightly more bolus insulin, albeit non-significantly, used in the insulin glargine group; however, the total daily doses did not differ between groups (table 2).

The HRQoL questionnaire showed a significant difference between treatment groups in favour of insulin degludec versus insulin glargine for the SF-36 domain of bodily pain (estimated treatment difference 1·4 points [95% CI 0·1–2·7; p=0·0320]). The appendix shows additional SF-36 data.

Rates of overall, nocturnal, and diurnal confirmed hypoglycaemia were significantly lower in patients treated with insulin degludec than with insulin glargine (figure 3). Rates of overall confirmed hypoglycaemia were 11·09 episodes per patient-year exposure with insulin degludec and 13·63 with insulin glargine; the

	Insulin degludec once-daily group (n=744)	Insulin glargine once-daily group (n=248)
Sex, male	405 (54%)	133 (54%)
Race		
White	619 (83%)	203 (82%)
Black	67 (9%)	27 (11%)
Asian	50 (7%)	13 (5%)
Other	8 (1%)	5 (2%)
Hispanic or Latin American ethnic origin	87 (12%)	32 (13%)
Age, years	59·2 (9·1)	58·1 (10·0)
Weight, kg	92·6 (17·9)	92·2 (17·2)
Body-mass index, kg/m²	32·3 (4·7)	31·9 (4·5)
Duration of diabetes, years	13·6 (7·4)	13·4 (6·9)
HbA_{1c}, %	8·3% (0·8)	8·4% (0·9)
HbA_{1c}, mmol/mol*	67 (8·7)	68 (9·8)
Fasting plasma glucose, mmol/L	9·2 (3·0)	9·2 (3·2)
Diastolic blood pressure, mm Hg†	76·7 (9·5)	77·4 (8·0)
Systolic blood pressure, mm Hg†	132·8 (15·2)	132·8 (14·0)
HDL cholesterol, mmol/L†	1·2 (0·3)	1·3 (0·4)
LDL cholesterol, mmol/L†	2·5 (0·9)	2·5 (0·9)
Triglycerides, mmol/L†	2·0 (1·4)	1·8 (1·2)
Insulin regimen		
Basal-bolus insulin±OAD	362 (49%)	124 (50%)
Basal-bolus insulin (<2 per day)±OAD	19 (3%)	3 (1%)
Premix therapy±OAD	181 (24%)	61 (25%)
Basal insulin±OAD	154 (21%)	56 (23%)
Bolus insulin±OAD	28 (4%)	4 (2%)
OAD regimen		
One	340 (46%)	130 (52%)
Two	124 (17%)	28 (11%)
More than two	15 (2%)	7 (3%)
OAD permitted during the trial		
Metformin alone or in combination	433 (58%)	151 (61%)
Pioglitazone alone or in combination	49 (7%)	12 (5%)

Data are n (%) or mean (SD), unless otherwise stated. OAD=oral antidiabetic drugs. *HbA_{1c} concentration in mmol/mol = (HbA_{1c} % – 2·15) × 10·929. †Data for the safety analysis group (753 patients who received insulin degludec and 251 who received insulin glargine).

Table 1: **Demographics and baseline characteristics of patients in the full analysis set**

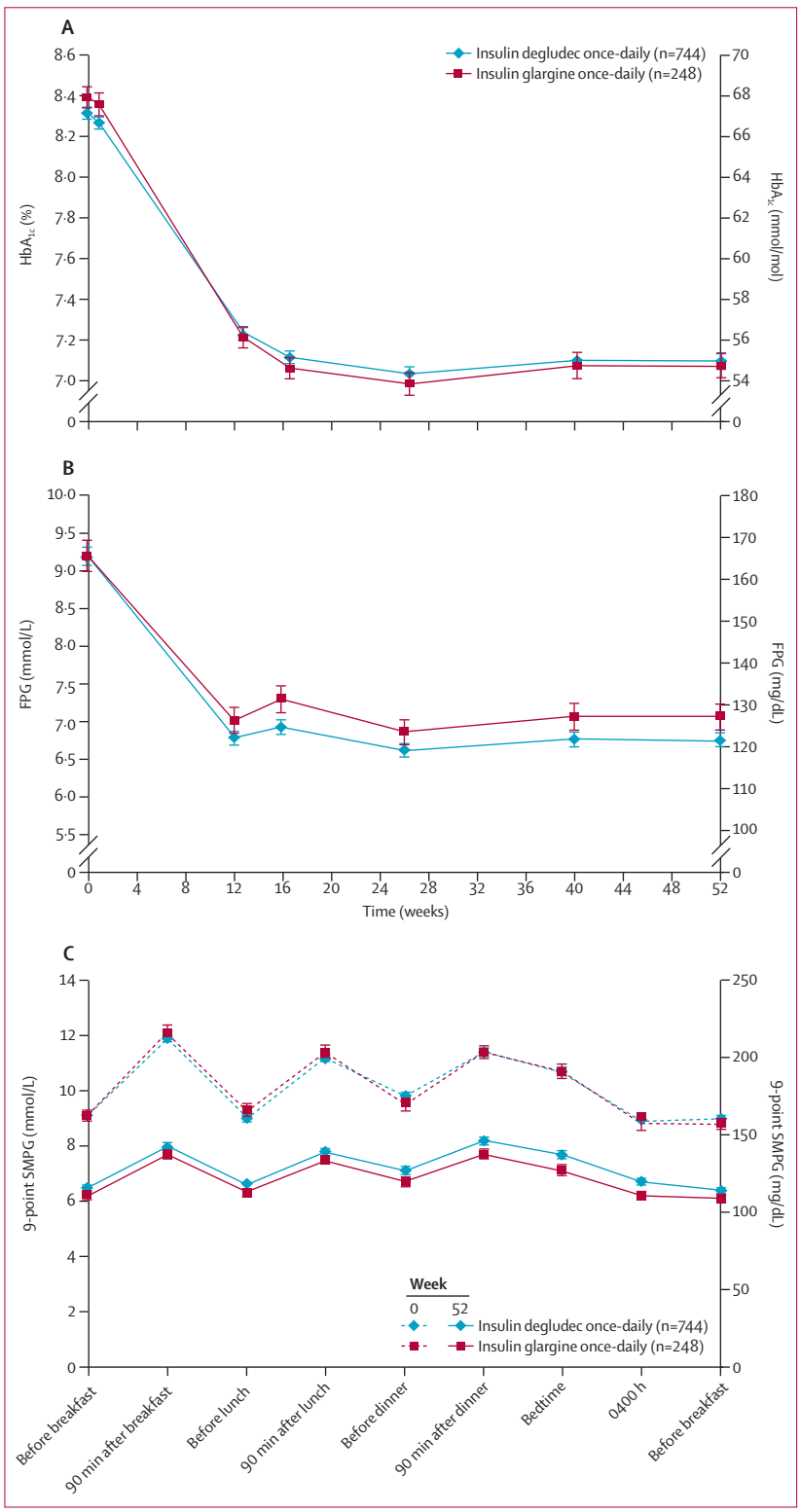

Figure 2: **Glycaemic efficacy and insulin dose in the full analysis set**
Data are mean (SE). (A) Mean HbA_{1c} during treatment. (B) Mean fasting plasma glucose during treatment. (C) 9-point profiles from self-measured plasma glucose at baseline (week 0) and after 52 weeks. Missing post-baseline data were imputed with the last observation carried forward approach. FPG=fasting plasma glucose. HbA_{1c}=glycated haemoglobin. SMPG=self-measured fasting plasma glucose.

estimated rate ratio was 0·82 (95% CI 0·69–0·99; p=0·0359) in favour of insulin degludec (table 3). Results were consistent in a post-hoc analysis that assessed confirmed hypoglycaemic episodes occurring during the maintenance period from week 16 to 52 (rate ratio 0·82, 95% CI 0·69–1·01; p=0·06). Too few severe hypoglycaemic events occurred for differences between groups to be assessed (table 3). The proportions of participants with confirmed hypoglycaemic events were similar with insulin degludec (609 [81%] of 753 participants) and insulin glargine (206 [82%] of 251 participants; table 3). The rate of nocturnal confirmed hypoglycaemia was 1·39 episodes per patient-year exposure for insulin degludec and 1·84 for insulin glargine (table 3). The rate ratio for nocturnal confirmed hypoglycaemic episodes was 0·75 (0·58–0·99, p=0·0399) in favour of insulin degludec (table 3) and post-hoc analysis suggested very similar results for episodes during the maintenance period from week 16 to week 52 (0·72, 0·51–0·99; p=0·0493).

586 (78%) of 753 of participants in the insulin degludec group and 198 (79%) of 251 participants in the insulin glargine group reported diurnal confirmed hypoglycaemic episodes. However, in post-hoc analysis, 9·28 such episodes occurred per patient-year exposure in the insulin degludec group compared with 11·39 in the insulin glargine group (rate ratio 0·82, 95% CI 0·684–0·995; p=0·044). The cumulative number of hypoglycaemic episodes per participant in 24 h seemed lower for insulin degludec than for insulin glargine (figure 3). More than 80% of trial participants had one or more episodes of hypoglycaemia; the small number of participants with very frequent episodes was evenly distributed between treatments (figure 3).

Reported mean weight gain at the end of the trial was similar in both groups (3·6 kg [SD 4·9] with insulin degludec and 4·0 kg [4·6] with insulin glargine). No differences were noted in laboratory measurements, physical examination, vital signs, ECG, or fundoscopy.

The proportion of participants reporting treatment-emergent adverse events did not differ between groups (610 [81%] of 753 participants in the insulin degludec group *vs* 199 [79%] of 251 participants in the insulin glargine group), as were proportion of patients withdrawn due to adverse events (31 [4%] in the insulin degludec group *vs* nine [4%] in the insulin glargine group; appendix). The most frequently reported adverse events in both treatment groups were nasopharyngitis, upper respiratory tract infection, and headache (table 4, appendix). Most adverse events were mild or moderate. Hypoglycaemia was the most frequently reported severe event possibly or probably related to the drug in both groups (20 [3%] of 753 participants in the insulin degludec group and seven [3%] of 251 in the insulin glargine group). Few participants reported injection-site reactions with insulin degludec (27 [4%] of 753 participants) or insulin glargine (seven [3%] of 251 participants).

	Insulin degludec once-daily group (U/kg; n=753)	Insulin glargine once-daily group (U/kg; n=251)	Unadjusted mean ratio	Estimated treatment ratio (95% CI)*
Basal				
Week 1	0·45 (0·25)	0·44 (0·27)	..	..
Week 52	0·75 (0·43)	0·69 (0·40)	1·08	1·08 (1·01–1·15)†
Bolus (daily insulin aspart at meals)				
Week 1	0·36 (0·29)	0·35 (0·29)	..	..
Week 52	0·72 (0·58)	0·74 (0·58)	0·98	0·97 (0·89–1·07)
Total (basal and bolus)				
Week 1	0·80 (0·44)	0·79 (0·46)	..	..
Week 52	1·46 (0·92)	1·42 (0·89)	1·03	1·03 (0·97–1·10)

Data are observed mean (SD) and week 52 values are presented with the last observation carried forward approach. *We adjusted estimated treatment ratios using ANOVA with treatment, sex, antidiabetic therapy at screening, age, and baseline dose as covariates. †p=0·0279.

Table 2: **Daily insulin dose for patients in the safety analysis set**

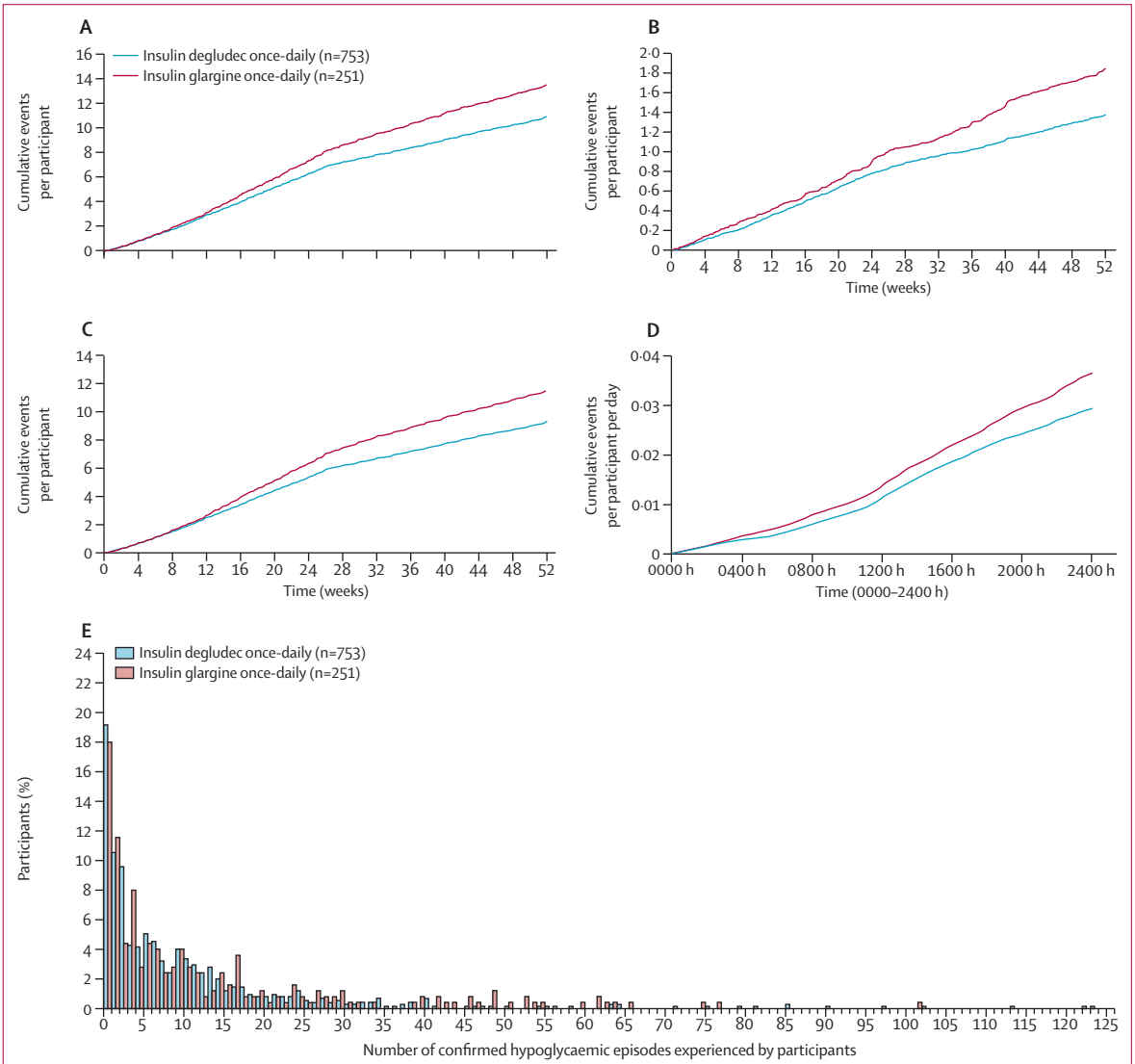

Figure 3: **Confirmed hypoglycaemic episodes in the safety analysis set**
(A) Overall confirmed hypoglycaemic episodes. (B) Nocturnal confirmed hypoglycaemic episodes. (C) Diurnal confirmed hypoglycaemic episodes. (D) Cumulative number of hypoglycaemic episodes per participant during 24 h. (E) Distribution of confirmed hypoglycaemic episodes.

	Insulin degludec once-daily group, U/kg (n=753)			Insulin glargine once-daily group, U/kg (n=251)			Estimated rate ratio insulin degludec:insulin glargine (95% CI)	p value
	Participants (%)	Episodes	Rate per PYE	Participants (%)	Episodes	Rate per PYE		
Severe*	34 (5%)	41	0·06	11 (4%)	12	0·05	..	..
Overall confirmed	609 (81%)	7437	11·09	206 (82%)	3120	13·63	0·82 (0·69–0·99)	0·0359
Nocturnal confirmed	298 (40%)	930	1·39	119 (47%)	422	1·84	0·75 (0·58–0·99)	0·0399

PYE=patient-year of exposure. *Insufficient episodes for statistical assessment.

Table 3: **Hypoglycaemic episodes**

	Insulin degludec once-daily group (n=753)			Insulin glargine once-daily group (n=251)		
	Participants (%)	Events	Event rate per 100 PYE	Participants (%)	Events	Event rate per 100 PYE
Infections						
Influenza	42 (6%)	45	7	15 (6%)	18	8
Nasopharyngitis	107 (14%)	146	22	35 (14%)	49	21
Upper respiratory tract infection	107 (14%)	156	23	32 (13%)	49	21
Musculoskeletal and connective tissue disorders						
Arthralgia	32 (4%)	38	6	20 (8%)	29	13
Back pain	41 (5%)	47	7	18 (7%)	20	9
Pain in limb	38 (5%)	43	6	14 (6%)	14	6
Nervous system disorders						
Headache	65 (9%)	129	19	18 (7%)	27	12
Gastrointestinal disorders						
Diarrhoea	46 (6%)	54	8	20 (8%)	22	10
General disorders and administration-site disorders						
Peripheral oedema	45 (6%)	54	8	14 (6%)	16	7
Injury, poisoning, and procedural complications						
Wrong drug administered	56 (7%)	61	9	8 (3%)	8	3
Respiratory, thoracic, and mediastinal disorders						
Cough	44 (6%)	46	7	16 (6%)	21	9
Vascular disorders						
Hypertension	41 (5%)	45	7	13 (5%)	13	6

PYE=patient-years of exposure.

Table 4: **Treatment-emergent adverse events reported by 5% or more of participants**

Rates of serious adverse events did not differ between treatment groups (21 events per 100 patient-years of exposure to insulin degludec and 20 events per 100 patient-years of exposure to insulin glargine), as was the distribution of serious adverse events (appendix). Ten participants died (eight [1%] of 753 participants in the insulin degludec group and two [1%] of 251 in the insulin glargine group; appendix). Investigators judged that no deaths were related to trial products, apart from the myocardial infarction reported in the insulin glargine group. Table 5 lists causes of death in the safety analysis set. No serious adverse events were deemed to be related to the injection devices by investigators in either treatment group. Rates of adjudicated cardiovascular events did not differ between groups (three events per 100 patient-years of exposure in the insulin degludec group *vs* two per 100 patient-years of exposure in the insulin glargine group).

Discussion

In participants with advanced insulin-treated type 2 diabetes mellitus, overall glycaemic reductions as measured by HbA_{1c} concentration resulting from basal-bolus intensive insulin therapy with insulin degludec were non-inferior to those noted for insulin glargine, which was to be expected from the treat-to-target trial design.[11] Treat-to-target trials allow investigators to minimise potential differences between treatments in measures of plasma glucose and can show differences in safety variables, including hypoglycaemia, in the presence of equivalent glycaemic control. This approach is in line with the US Food and Drug Administration's regulatory guidance for insulin clinical trials, which

states, "similar degrees of glycemic control (test non-inferior to reference) should be achieved so that comparisons among groups in frequency and severity of hypoglycemia will be interpretable in ultimate risk-benefit assessments".[11]

Reduction of the risk of hypoglycaemia has been a central theme in the management of patients with type 1 diabetes mellitus. In view of the lower rates of hypoglycaemia noted in type 2 diabetes mellitus than in type 1 diabetes mellitus, hypoglycaemia as a barrier to glycaemic control or as a predictor of adverse outcomes has, in the past, been neglected as a point of investigation in type 2 disease. However, Banarer and Cryer have postulated that, because of the loss of insulin secretion in advanced type 2 diabetes mellitus, hypoglycaemia is a progressively more common clinical issue (approximating that in type 1 disease) as patients approach the insulin-deficient end of the spectrum of type 2 diabetes.[12] Results from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study[13] showed that hypoglycaemia was an independent predictor of mortality in patients with type 2 diabetes mellitus. In the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE)[14] and Veterans Affairs Diabetes Trial (VADT)[15] studies, a recent episode of severe hypoglycaemia was a predictor for cardiovascular death and all-cause mortality, as well as an increased risk of adverse clinical outcomes (major macrovascular and microvascular events). Hypoglycaemic events have been linked to an increased risk of acute cardiovascular events in a study of health-care claims data[16] and can produce electrocardiographic changes that are associated with fatal cardiac arrhythmias.[17] On the basis of these results, we suggest a causal relation between increased rates of hypoglycaemic events and the potential for increased morbidity and mortality in type 2 diabetes mellitus.

Hypoglycaemic symptoms alone are unreliable as a guide for quantification of hypoglycaemic episodes because patients develop symptoms at very variable blood glucose concentrations. Therefore, for the purposes of this trial, confirmed hypoglycaemia (plasma glucose <3·1 mmol/L or severe episodes requiring assistance) was chosen as a safety endpoint because such episodes are definitively linked to low glucose concentrations. Many of the documented hypoglycaemic episodes were detected incidentally by protocol-specified monitoring of plasma glucose concentrations and others were prompted by hypoglycaemic symptoms that led to the detection and reporting of hypoglycaemia. Thus, rates of hypoglycaemia in this trial, as in most trials of type 2 diabetes mellitus could overestimate or underestimate the true rates, because some asymptomatic events could have been missed and others detected only because of protocol-specified monitoring. To ensure that most hypoglycaemic episodes were captured in this trial, episodes were reported to the investigators weekly (weeks 0–26) or fortnightly (weeks 26–52). Although there were too few severe episodes in this trial for statistical comparison, rates seemed similar between the insulin degludec and insulin glargine groups; therefore, the significantly lower rates of overall and nocturnal confirmed hypoglycaemia were due to self-treated rather than severe hypoglycaemic episodes.

	Age, years	Sex	Trial day of adverse event onset	Cause of death
Insulin degludec group (n=753)				
Patient 1	65	Male	78	Arteriosclerosis and hypertensive heart disease
Patient 2	58	Male	82	Myocardial infarction
Patient 3	69	Male	86	Intracranial haemorrhage
Patient 4	63	Male	10	Cardiorespiratory arrest
Patient 5	68	Male	227	Haematemesis
Patient 6	67	Female	34	Cardiac arrest
Patient 7	54	Male	45	Rectal haemorrhage, anaemia, and myocardial infarction
Patient 8	58	Male	20	Road traffic accident
Insulin glargine group (n=251)				
Patient 9	61	Male	123	Metastatic neoplasm
Patient 10	48	Male	336	Myocardial infarction*

*Investigator assessed this event as possibly related to trial products.

Table 5: **Causes of death in the safety analysis set**

The lower rates of hypoglycaemia reported in this trial with insulin degludec than with insulin glargine are an improvement of the same magnitude as was reported in the original treat-to-target trials comparing the first basal insulin analogues with neutral protamine Hagedorn (NPH; panel).[19,21] A significant difference in the rate of hypoglycaemia (at the same degree of glycaemic control) between insulin degludec and insulin glargine is clinically relevant because up to 80% of doctors report that fear of hypoglycaemia hinders the initiation and intensification of their patients' insulin treatment.[22,23] Moreover, patients also have the same fears, which can lead to the persistence of higher glucose concentrations overall or failure to use adequate doses of insulin.[23,24] Moreover, symptoms of hypoglycaemia can adversely affect HRQoL, specifically pain or discomfort and anxiety or depression.[25] Nocturnal hypoglycaemia is of clinical concern because many episodes are asymptomatic and can go undetected until episodes become severe.[24,26] In addition to potential adverse clinical effects, a 2011 survey suggested that non-severe nocturnal hypoglycaemic events can negatively affect work productivity and routine daily functions in patients with type 2 diabetes mellitus.[27]

In this trial, most hypoglycaemic events in both treatment groups occurred during daytime hours, probably reflecting the contribution of bolus mealtime insulin. Only 10–15% of hypoglycaemic events were recorded at night. This small proportion of nocturnal events might reflect a reduced potential of basal insulin to produce hypoglycaemia, the absence of symptoms to trigger blood glucose monitoring during those hours, or both. Despite the low rates of nocturnal hypoglycaemic

Panel: **Research in context**

Systematic review

We searched Medline for meta-analyses or reviews published in English between August, 2009, and August, 2011, with the terms "basal bolus" AND "type 2 diabetes" AND "insulin detemir" AND "insulin glargine". No criteria to assess quality were set.

Interpretation

Insulin management in type 2 diabetes mellitus has, in some ways, changed little in the past 25 years. Traditionally, insulin was added to failed oral antidiabetic drug regimens, usually at bedtime.[18] Animal and human neutral protamine Hagedorn (NPH) insulins proved to function poorly as a basal insulin for this purpose. Other approaches used ultralente insulin, as in the UK Prospective Diabetes Study,[1] with somewhat greater success (especially as monotherapy). However, because of undesirable adverse effects and dislike of insulin injections, patients and practitioners sought other means of attaining glycaemic control. The first longacting basal insulin analogue, insulin glargine, fundamentally changed insulin treatment in type 2 diabetes mellitus. In a randomised, prospective, treat-to-target trial, rates of nocturnal hypoglycaemia were lower with insulin glargine than with NPH insulin, with the same glycaemic control and equal weight gain.[19] The longacting insulin analogue, insulin detemir, has proved to be non-inferior—but not superior—to insulin glargine in most trials.[20]

One of the drawbacks of basal insulin therapy is that it does not stop the loss of β-cell function, which is the hallmark of type 2 diabetes mellitus. Therefore, as β-cell function declines and postprandial hyperglycaemia worsens, diabetes control inevitably deteriorates despite continuing basal insulin titration. In this trial, we examined the efficacy and safety of a new, ultra-longacting basal insulin analogue, insulin degludec, which has previously been shown to have a flat pharmacokinetic profile, in combination with rapid-acting mealtime bolus insulin aspart for advanced cases of type 2 diabetes. Despite the important contribution of mealtime insulin toward overall hypoglycaemia, rates of overall and nocturnal hypoglycaemia were significantly lower with insulin degludec than with insulin glargine. The lower rate of hypoglycaemia is a step forward in insulin management of type 2 diabetes similar to the original treat-to-target trial comparing NPH with insulin glargine.[19]

events reported in this study, and consistent with the diurnal hypoglycaemia results, the difference between the basal insulins was significant. Because no difference was noted in overall glycaemic control as shown by HbA_{1c} concentrations, the significantly reduced rate of overall confirmed hypoglycaemia seems to suggest actual differences in the pharmacodynamic and pharmacokinetic properties of the two insulins in the setting of clinical diabetes management.

Limitations to this trial include the open-label design, which could have affected patient-reported outcomes. Another limitation was that the masked titration committee did not enforce a uniform titration algorithm for bolus insulin aspart, as it did for the basal insulins (insulin degludec and glargine). Therefore, titration of bolus insulin might not have been uniform and adequate, which could have increased prandial excursions and restricted the proportion of patients achieving HbA_{1c} targets in both groups. Another factor that might have affected the results was the titration target for basal insulin before breakfast SMPG of 3·9–<5·0 mmol/L. This titration target provided superior glycaemic efficacy elsewhere compared with the higher titration target of 4·4–6·1 mmol/L, with a low rate of hypoglycaemia.[28] Furthermore, the expectation was that an insulin with a flat and stable profile would allow a target close to normoglycaemia to be reached for SMPG before breakfast with low risk of hypoglycaemia. Notwithstanding, the basal insulin dose was ultimately chosen by the investigator, who could use clinical judgment to override titration recommendations. That final fasting plasma glucose values in both groups were greater than 5 mmol/L in this open-label trial suggests that investigators were reluctant to follow the titration algorithm, possibly due to unease with target or attained plasma glucose concentrations or fear of hypoglycaemia. The timing of the administration of both basal insulins could have also affected the outcomes but this effect is unlikely because insulin glargine was given according to product labelling (ie, any time of the day as deemed necessary by the investigator, but at the same time each day); thus, if time of dosing had any effect, it would have reduced nocturnal hypoglycaemia. Therefore, the most probable explanation for the difference in nocturnal hypoglycaemia lies in the pharmacodynamic properties of these two basal insulins, with insulin degludec having a longer, flatter, and more stable profile than insulin glargine.[3,4] The significantly lower rate of nocturnal hypoglycaemia with insulin degludec while achieving similar glycaemic control, might offer a safer option in patients with longstanding type 2 diabetes mellitus who need basal-bolus insulin therapy.

Contributors

AJG, ABK, SDP, SS, MKB, MM-T, JR, and PH were trial investigators and helped obtain data. AJG and PH prepared the first draft of the manuscript. AJG wrote the research in context panel. AMOF was responsible for medical oversight during the trial. LAE was responsible for the statistical considerations in the analysis and trial design. All authors participated in reviewing and interpreting the data, generating post-hoc analyses, and providing further comments and revisions to the manuscript. All authors approved the final version of the manuscript and take full responsibility for the content.

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Conflicts of interest

AJG has served as a consultant on advisory boards or panels for GlaxoSmithKline, Novo Nordisk, Merck, and Daiichi-Sankyo, Takeda, LipoScience, and Boehringer Ingelheim and speakers' bureaux for GlaxoSmithKline, Merck, Novo Nordisk, Santarus, and Daiichi-Sankyo. AJG is on the American Association of Clinical Endocrinologists board of directors. ABK has participated in speakers' bureaux for Novo Nordisk, Eli Lilly, Amylin Pharmaceuticals, Animas Corporation, and Sanofi-Aventis and has received research support from Novo Nordisk, Eli Lilly, Amylin Pharmaceuticals, Animas Corporation, Sanofi-Aventis, and Medtronic. SDP has served on scientific advisory boards and received honoraria or consulting fees and has received grants or research support from insulin manufacturers, Novo Nordisk, Eli Lilly, and Sanofi-Aventis. SS has received grant support from Novo Nordisk and Sanofi-Aventis and is a member of local advisory boards for Novo Nordisk, Merck, Novartis, Bristol-Myers Squibb, and Eli Lilly. MKB and

MM-T declare that they have no conflicts of interest. JR has served on scientific advisory boards and received honoraria or consulting fees and grants or research support from insulin manufacturers, Novo Nordisk, Eli Lilly, Sanofi-Aventis and MannKind. LAE and AMOF are employees of Novo Nordisk and own stock in the company. PH has served on advisory boards for Novo Nordisk, Roche, Orexigen, and Pfizer. The authors received no payment for writing or contributing to this report.

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