

Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial



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Summary

Background Intensive basal-bolus insulin therapy has been shown to improve glycaemic control and reduce the risk of long-term complications that are associated with type 1 diabetes mellitus. Insulin degludec is a new, ultra-longacting basal insulin. We therefore compared the efficacy and safety of insulin degludec and insulin glargine, both administered once daily with mealtime insulin aspart, in basal-bolus therapy for type 1 diabetes.

Methods In an open-label, treat-to-target, non-inferiority trial, undertaken at 79 sites (hospitals and centres) in six countries, adults (aged ≥ 18 years) with type 1 diabetes (glycated haemoglobin [HbA_{1c}] $\leq 10\%$ [86 mmol/mol]), who had been treated with basal-bolus insulin for at least 1 year, were randomly assigned in a 3:1 ratio, with a computer-generated blocked allocation sequence, to insulin degludec or insulin glargine without stratification by use of a central interactive response system. The primary outcome was non-inferiority of degludec to glargine, assessed as a reduction in HbA_{1c} after 52 weeks, with the intention-to-treat analysis. This trial is registered with ClinicalTrials.gov, number NCT00982228.

Findings Of 629 participants, 472 were randomly assigned to insulin degludec and 157 to insulin glargine; all were analysed in their respective treatment groups. At 1 year, HbA_{1c} had fallen by 0.40% points (SE 0.03) and 0.39% points (0.07), respectively, with insulin degludec and insulin glargine (estimated treatment difference -0.01% points [95% CI -0.14 to 0.11]; $p < 0.0001$ for non-inferiority testing) and 188 (40%) and 67 (43%) participants achieved a target HbA_{1c} of less than 7% ($< 53 \text{ mmol/mol}$). Rates of overall confirmed hypoglycaemia (plasma glucose $< 3.1 \text{ mmol/L}$ or severe) were similar in the insulin degludec and insulin glargine groups (42.54 vs 40.18 episodes per patient-year of exposure; estimated rate ratio [degludec to glargine] 1.07 [0.89 to 1.28]; $p = 0.48$). The rate of nocturnal confirmed hypoglycaemia was 25% lower with degludec than with glargine (4.41 vs 5.86 episodes per patient-year of exposure; 0.75 [0.59 to 0.96]; $p = 0.021$). Overall serious adverse event rates (14 vs 16 events per 100 patient-years of exposure) were similar for the insulin degludec and insulin glargine groups.

Interpretation Insulin degludec might be a useful basal insulin for patients with type 1 diabetes because it provides effective glycaemic control while lowering the risk of nocturnal hypoglycaemia, which is a major limitation of insulin therapy.

Funding Novo Nordisk.

Introduction

The physiological replacement of insulin in patients with type 1 diabetes mellitus is challenging because exogenous insulin needs to cover both basal and meal-related (bolus) insulin requirements. In landmark trials, intensive basal-bolus therapy was successful in improving glycaemic control and reducing the risk of long-term complications that are associated with type 1 diabetes mellitus.^{1,2}

The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) recommend a glycated haemoglobin (HbA_{1c}) target of less than 7% ($< 53 \text{ mmol/mol}$), without substantial hypoglycaemia.^{3,4} A history of hypoglycaemia and the fear of further episodes, particularly at night, can lead to poor adherence to treatment and compromise glycaemic control.⁵⁻⁸ Nocturnal hypoglycaemia is associated with

poor quality of sleep, decreased sense of wellbeing, fatigue, and reduced productivity.^{5,7,9,10}

The risk of hypoglycaemia is partly due to impaired protective endocrine and physiological responses but limitations in subcutaneous insulin delivery contribute substantially to hypoglycaemic risk. Subcutaneous absorption is not reproducible and insulin entry directly into the peripheral circulation (bypassing portal circulation) is not linked to glucose sensing. Insulin analogues have been developed to improve the physiological coverage of the need for insulin. Basal insulin analogues such as insulin glargine and insulin detemir have longer duration of action and lower risks of hypoglycaemia than neutral protamine Hagedorn insulin, especially at night.¹¹ However, neither insulin reliably provides 24 h basal insulin replacement on all

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days in all patients with type 1 diabetes mellitus, and once-daily dosing with these analogues can be inadequate; thus, an insulin with a more predictable and longer duration of action is needed.¹²

Insulin degludec is an ultra-longacting insulin that is in clinical development. On subcutaneous injection, it forms a depot of soluble multihexamers from which insulin is slowly and continuously absorbed into the circulation.¹³ Pharmacokinetic data show that insulin degludec has a flat, stable profile at steady state and a terminal half-life of more than 25 h, which is twice that of insulin glargine, and a duration of action greater than 40 h.^{13,14} In a phase 2 trial, glycaemic control with insulin degludec in patients with type 1 diabetes mellitus was similar to that with insulin glargine but the rate of hypoglycaemia was lower,¹⁵ perhaps because in pharmacodynamic studies the day-to-day variability with insulin degludec was four times lower.¹⁶

We compared the efficacy and safety of insulin degludec with that of insulin glargine, both administered once daily in a basal-bolus regimen with rapid-acting insulin aspart as meal-time insulin in participants with type 1 diabetes mellitus in this BEGIN Basal-Bolus Type 1 trial.

Methods

Study design and participants

In a 52 week, randomised, controlled, open-label, multinational, parallel design, treat-to-target, non-inferiority trial, participants with type 1 diabetes mellitus were given insulin degludec or insulin glargine, with insulin aspart as the meal-time insulin. The trial was undertaken at 79 sites that were university-affiliated, public and private hospitals and clinical research centres in six countries (France, Germany, Russia, South Africa, the UK, and the USA).

Adults (aged ≥ 18 years) who had been diagnosed with type 1 diabetes mellitus for at least 1 year and had received any basal-bolus insulin therapy for at least 1 year before screening, with HbA_{1c} of 10% (86 mmol/mol) or less and body-mass index of 35 kg/m² or less were eligible for participation in this study. The complete inclusion and exclusion criteria are provided in the appendix p 1.

The trial was done in accordance with the Declaration of Helsinki¹⁷ and Good Clinical Practice Guidelines.¹⁸ Signed informed consent was obtained from each participant. The protocol and the consent form were reviewed and approved by the local independent ethics committee or institutional review board before trial initiation.

Randomisation and masking

Eligible participants were randomly assigned in a 3:1 ratio to once-daily insulin degludec (100 U/mL, subcutaneously, 3 mL FlexPen, insulin and insulin pen manufactured by Novo Nordisk, Bagsværd, Denmark) or insulin glargine (Lantus, 100 U/mL, subcutaneously, 3 mL SoloStar, insulin and insulin pen manufactured by Sanofi, Paris, France), both in combination with meal-time insulin aspart

(NovoRapid/NovoLog, 100 U/mL, subcutaneously, 3 mL FlexPen, Novo Nordisk, Bagsværd, Denmark), by means of a central interactive voice or web response system. The random allocation scheme was computer generated using blocks. The allocation sequence was generated by trained personnel in clinical supplies labelling and information technology. The investigators enrolled the eligible participants. The 3:1 randomisation ratio ensured adequate exposure to insulin degludec, as required by regulatory guidelines.¹⁹ This study was open label, with participants and investigators not masked to treatment because the injection devices were different. However, masking of the trial products was maintained for the titration surveillance committee and everyone involved in defining the analysis sets until the database was locked for statistical analysis. Continuous safety surveillance in these trials was done by an internal masked Novo Nordisk Safety Committee and an independent ad-hoc group was to be established to maintain masking if the committee requested unmasking. An independent, external, masked event adjudication committee adjudicated cardiovascular events in accordance with predefined classifications.

Procedures

Eligible participants were switched from their long-term basal-bolus insulin therapy to once-daily insulin degludec or insulin glargine with mealtime insulin aspart at randomisation (week 0). If previous basal insulin was used once daily, initial doses were replaced with insulin degludec or insulin glargine in a 1:1 ratio. If more than one daily dose had been taken, the total daily basal dose was calculated and replaced with insulin degludec in a 1:1 ratio, with the recommendation that the dose be reduced by 20–30% for patients in the insulin glargine group, and administered once daily, as per approved prescribing information. Insulin degludec was administered once daily with the main evening meal and insulin glargine was administered according to approved labelling (once daily at any time but at the same time every day throughout the study). Participants switched their pretrial bolus insulin to insulin aspart in a 1:1 ratio. Insulin aspart was taken before each meal (breakfast, lunch, and dinner). Additional doses were allowed with a fourth meal and snacks. At the end of the treatment, basal insulin was switched to neutral protamine Hagedorn insulin to minimise interference with antibody detection at the follow-up visit 1 week later.

A treat-to-target approach was used throughout the study to ensure optimum titration. Changes to basal insulin were recommended before changes to the bolus insulin were considered. The basal insulin dose was titrated with the aim of achieving before-breakfast self-measured plasma glucose (SMPG) concentration of 3.9 mmol/L to less than 5.0 mmol/L. The bolus insulin doses were titrated with the aim of achieving preprandial (of next meal) and bedtime SMPG concentrations of 3.9 mmol/L to less than 5.0 mmol/L. Details, including titration algorithms, are provided in appendix pp 2–6.

See Online for appendix

Safety variables were adverse events, hypoglycaemic episodes, insulin dose, bodyweight, injection-site reactions, abnormal findings related to physical examination, vital signs, funduscopy, electrocardiogram (ECG), and laboratory tests (including antibodies). Confirmed hypoglycaemic episodes included those with a plasma glucose concentration of less than 3·1 mmol/L or severe episodes necessitating assistance³ (appendix p 7). Hypoglycaemic episodes occurring from 0001 h and 0559 h were classified as nocturnal and those occurring from 0600 h and 0000 h were classified as diurnal.

Laboratory analyses were undertaken at the commercial central laboratories (Quintiles Laboratories Europe, West Lothian, UK, Quintiles Laboratories South Africa, Irene, South Africa, Quintiles Laboratories, Marietta, GA, USA). Antibodies were analysed at Celerion Switzerland, Fehraltorf, Switzerland, by a validated subtraction radioimmunoassay method.^{20,21}

Statistical analysis

The primary objective was to confirm the non-inferiority of insulin degludec to insulin glargine in reduction in HbA_{1c} from baseline after 52 weeks of treatment.¹⁹ Non-inferiority was confirmed if the upper limit of the 95% CI of the treatment difference was less than or equal to 0·4% points, as recommended by regulatory guidelines.

The type 1 error rate was controlled by use of a hierarchical (fixed-sequence) testing procedure for selected endpoints, including change in HbA_{1c} concentration, number of nocturnal confirmed and overall confirmed hypoglycaemic episodes, and change in fasting plasma glucose (FPG; appendix p 8). Sample size was determined by the primary objective with the assumption of a one-sided *t* test at a significance level of 2·5%, a zero mean treatment difference, and an SD of 1·1% for HbA_{1c}. A total of 624 participants were needed for at least 95% power after adjustment for a 15% dropout rate.

All participants randomly assigned treatment were included in the intention-to-treat statistical analyses of all efficacy endpoints (HbA_{1c}, FPG, SMPG, health-related quality of life [HRQoL]), hypoglycaemia, bodyweight, and lipids. All other safety endpoints were assessed in participants exposed to treatment. Missing values were imputed by the last observation carried forward approach.¹⁹ Statistical analyses were done with SAS software (version 9.1.3).

Baseline characteristics, demography, and adverse events were presented by use of descriptive statistics. Treatment differences in HbA_{1c}, FPG, SMPG, HRQoL, insulin dose, bodyweight, and lipid concentrations after 52 weeks of treatment were estimated by use of ANOVA, with treatment, antidiabetic treatment at screening (once-daily or more than once-daily basal injections [including pump]), sex, and region as fixed factors, and age and baseline values as covariates. Rate ratios of hypoglycaemic episodes were estimated by use of a negative binomial regression model with treatment, antidiabetic therapy at

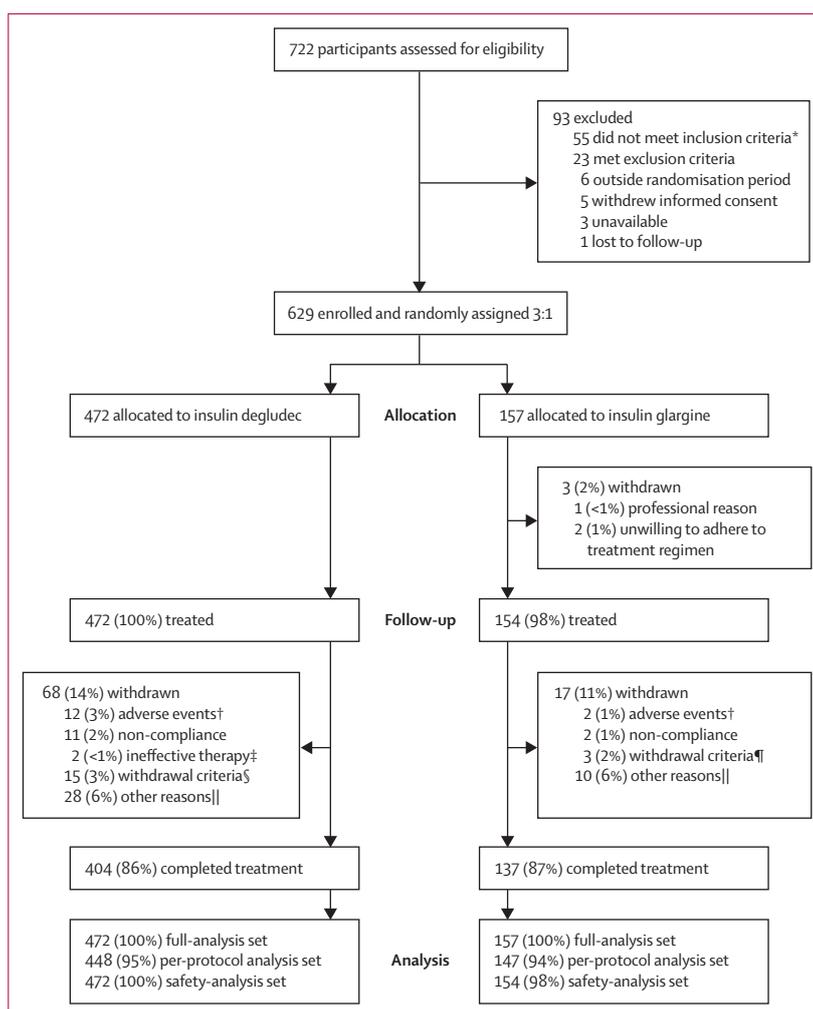


Figure 1: Trial profile

Full-analysis set included all randomly assigned participants. Safety-analysis set included participants exposed to treatment. Per-protocol analysis set included participants who complied with all recruitment criteria (ie, inclusion and exclusion criteria), had at least 12 weeks of exposure, and had valid assessments of glycated haemoglobin at baseline and at or after 12 weeks of treatment. *37 participants did not meet inclusion criteria of glycated haemoglobin of 10% (86 mmol/mol) or less. †See appendix p 9. ‡As judged by investigator. §Two participants were withdrawn because of lack of effect as per withdrawal criterion. ¶One participant was withdrawn because of lack of effect as per withdrawal criterion. ||See appendix p 9.

screening, sex, and region as fixed factors, and age as covariate, for all reported episodes that were assessed to be treatment-emergent in all randomly assigned participants (predefined analysis). To establish the hypoglycaemic profile after achievement of stable dose and glycaemic control for most participants, the model was also fitted in a post-hoc analysis of episodes occurring in the maintenance period from week 16 to week 52. The 9-point SMPG profile data were analysed with a repeated measures model. Prandial increments in plasma glucose were analysed by use of the ANOVA method described above. The time to first achieve SMPG before breakfast of less than 5·0 mmol/L was analysed by use of a Cox proportional hazards model. Insulin dose and diurnal confirmed hypoglycaemia were analysed post hoc. Data

	Insulin degludec	Insulin glargine
Full-analysis set	472	157
Safety-analysis set	472	154
Women	194 (41%)	67 (43%)
Race		
White	437 (93%)	148 (94%)
Black	9 (2%)	3 (2%)
Asian	6 (1%)	3 (2%)
Other	20 (4%)	3 (2%)
Ethnic origin		
Hispanic or Latin American	22 (5%)	10 (6%)
Non-Hispanic or non-Latino	450 (95%)	147 (94%)
Age (years)	42.8 (13.7)	43.7 (13.3)
Bodyweight (kg)	78.9 (14.3)	78.3 (16.2)
Body-mass index (kg/m ²)	26.3 (3.7)	26.4 (4.2)
Duration of diabetes (years)	19.1 (12.2)	18.2 (11.4)
HbA _{1c} (%)	7.7 (0.9)	7.7 (1.0)
HbA _{1c} (mmol/mol*)	60.7 (9.8)	60.7 (11.0)
FPG (mmol/L)	9.1 (4.0)	9.7 (4.4)
Diastolic blood pressure (mm Hg)	74.1 (8.4)	73.5 (7.9)
Systolic blood pressure (mm Hg)	121.8 (12.8)	119.2 (12.9)
HDL cholesterol (mmol/L)	1.57 (0.4)	1.60 (0.5)
LDL cholesterol (mmol/L)	2.51 (0.8)	2.47 (0.8)
Total cholesterol (mmol/L)	4.54 (0.9)	4.55 (0.9)
Triglycerides (mmol/L)	1.00 (0.9)	1.03 (0.7)
Basal insulin type at screening		
Glargine	334 (71%)	108 (69%)
Detemir	87 (18%)	34 (22%)
Neutral protamine Hagedorn	37 (8%)	12 (8%)
Other	2 (<1%)	..
Bolus insulin at screening		
Aspart	244 (52%)	81 (52%)
Lispro	183 (39%)	59 (38%)
Other	45 (10%)	17 (11%)

Data are number, number (%), or mean (SD). Data are for the full-analysis set, with the exception of lipids and blood pressure, which are for the safety-analysis set. Baseline values for FPG, HbA_{1c}, and lipids were recorded at the randomisation visit (week 0) and the others were recorded at the screening visit (1 week before randomisation). HbA_{1c}=glycated haemoglobin. FPG=fasting plasma glucose. *Calculated, not measured, by the formula: (HbA_{1c} [%]-2.15) × 10.929.

Table 1: Demographics and baseline characteristics of the randomly assigned population in the insulin degludec and insulin glargine groups

were reported with 95% CI and p values for two-sided testing at an α of 0.05.

This trial is registered with ClinicalTrials.gov, number NCT00982228.

Role of the funding source

The sponsor was responsible for the study design, supply of trial products and equipment, monitoring, data management, statistics, and preparation of the clinical trial report. All authors had access to trial data and had full responsibility for the content of the report and had final responsibility for the decision to submit for publication.

Results

626 of 629 participants who were randomly assigned to treatment between Sept 1, 2009, and Nov 8, 2010, were given one of the trial drugs, and most (404 [86%] of 472 in insulin degludec group and 137 [87%] of 157 in insulin glargine group) completed the trial (figure 1). The overall withdrawal pattern was similar in the two groups.

Baseline characteristics were representative of a population with type 1 diabetes mellitus with reasonably good glycaemic control (mean HbA_{1c} 7.7%, 60.7 mmol/mol, table 1). The antidiabetic regimen before the trial for most participants (455 [72%] of 629) consisted of once-daily basal injection with one or more bolus doses; insulin glargine and insulin aspart were the most commonly used pretrial basal and bolus insulins, used by 442 (70%) and 325 (52%) participants, respectively (table 1).

As would be expected with the treat-to-target method, the mean decrease in HbA_{1c} from baseline was similar between treatments (figure 2A; appendix p 10): 0.40% points (SE 0.03) for insulin degludec and 0.39% points (0.07) for glargine with an estimated treatment difference (ETD) of -0.01% points (95% CI -0.14 to 0.11; $p < 0.0001$ for one-sided test of non-inferiority evaluated at the 2.5% level). Thus, insulin degludec was non-inferior to insulin glargine in reducing HbA_{1c} concentrations. The robustness of the primary analysis was further supported by the results of the per-protocol set (-0.01% points [-0.14 to 0.12]) and additional sensitivity analyses (appendix p 11).

Similar proportions of participants achieved the ADA and EASD HbA_{1c} target (<7%, <53 mmol/mol) with insulin degludec (188 [40%] of 472) and insulin glargine (67 [43%] of 157). After 52 weeks of treatment, mean baseline FPG decreased by 1.3 mmol/L (SE 0.2) to 7.8 mmol/L (0.2) with insulin degludec and by 1.4 mmol/L (0.4) to 8.3 mmol/L (0.3) with insulin glargine. The mean reduction in laboratory-reported FPG (figure 2B; appendix p 10) was not significantly different between treatments, with an estimated treatment difference of -0.33 mmol/L (95% CI -1.03 to 0.36; $p = 0.35$). Mean 9-point SMPG profiles decreased in both groups (figure 2C). The mean SMPG before breakfast used for dose adjustment decreased from 8.6 mmol/L (0.1) at baseline to 7.3 mmol/L (0.1) with insulin degludec and from 8.6 mmol/L (0.2) to 7.8 mmol/L (0.2) with insulin glargine. The mean SMPG before breakfast was significantly lower with insulin degludec; estimated treatment difference between insulin degludec and insulin glargine was -0.55 mmol/L (-1.03 to -0.08; $p = 0.023$). Differences in the mean prandial increments after breakfast ($p = 0.70$), lunch ($p = 0.68$), and main evening meal ($p = 0.86$) were not significant (appendix p 11). The median time to first achieve the SMPG before breakfast of less than 5.0 mmol/L was 5 weeks (IQR 3-14) for participants treated with insulin degludec and 10 weeks (4-22) for those given insulin glargine (appendix p 12).

At end of trial, the mean values for daily basal, daily bolus, and daily total insulin doses were significantly

lower by 14%, 10%, and 11%, respectively, in the insulin degludec group relative to the insulin glargine group (table 2). Mean daily doses of insulin degludec changed little during the trial, and there was a substantial increase in insulin glargine in the first 5 weeks. The mean daily insulin aspart doses increased mostly during the first 12 weeks in both treatment groups (appendix p 13).

Mean weight gain was similar in both treatment groups: 1.8 kg (SE 0.2) with insulin degludec and 1.6 kg (0.3) with insulin glargine ($p=0.62$; appendix p 11, p 14). The rates of all confirmed hypoglycaemic episodes and diurnal confirmed hypoglycaemic episodes were similar in the two treatment groups (figure 3A; table 3). The lower rate of nocturnal confirmed hypoglycaemia with insulin degludec was apparent as early as 8 weeks after treatment initiation, and was significantly lower by 25% at the end of treatment. The rate of severe hypoglycaemic episodes was low and did not differ significantly between treatments (table 3). The rates of overall confirmed and nocturnal confirmed hypoglycaemic episodes were also analysed in participants during the maintenance phase (from week 16 to end of trial) when insulin doses and glycaemic indicators seemed to have stabilised for most participants. In the maintenance phase, the rate of confirmed hypoglycaemic episodes per patient-year of exposure was similar between the insulin degludec and insulin glargine groups (37.30 vs 36.22, estimated rate ratio of insulin degludec to insulin glargine 1.02 [95% CI 0.83–1.25]; $p=0.83$) and the rate of nocturnal confirmed hypoglycaemic episodes per patient-year of exposure was significantly lower by 27% with insulin degludec (3.91 vs 5.22, 0.73 [0.56–0.96]; $p=0.024$).

Adverse event rates were 438 per 100 patient-years of exposure (PYE) for insulin degludec and 432 per 100 PYE for insulin glargine (table 4). No treatment-specific patterns were seen (appendix p 15). Most adverse events (2377 [94%] of 2518) were mild or moderate and were thought to be unrelated to basal insulin by the investigator (2315 [92%]; table 4; appendix p 30). The rate of injection-site reactions was low in both groups (table 4) and none were severe.

Rates of serious adverse events per 100 PYE were similar between the insulin degludec and insulin glargine groups. The distribution of the number of serious adverse events was similar in the two treatment groups (appendix p 25) and most participants in the insulin degludec (423 [90%] of 472) and insulin glargine (137 [89%] of 154) groups reported no serious adverse events. The most frequently reported serious adverse events related to basal insulin were hypoglycaemia, hypoglycaemic unconsciousness, and hypoglycaemic seizure (appendix p 26). Four serious adverse events were adjudicated as major adverse cardiovascular events, of which three were fatal. One serious adverse event of sudden death was in a 26-year-old woman who was found dead in bed after 32 days of treatment; her medical history included diabetes and asthma. The death was judged to be related to insulin

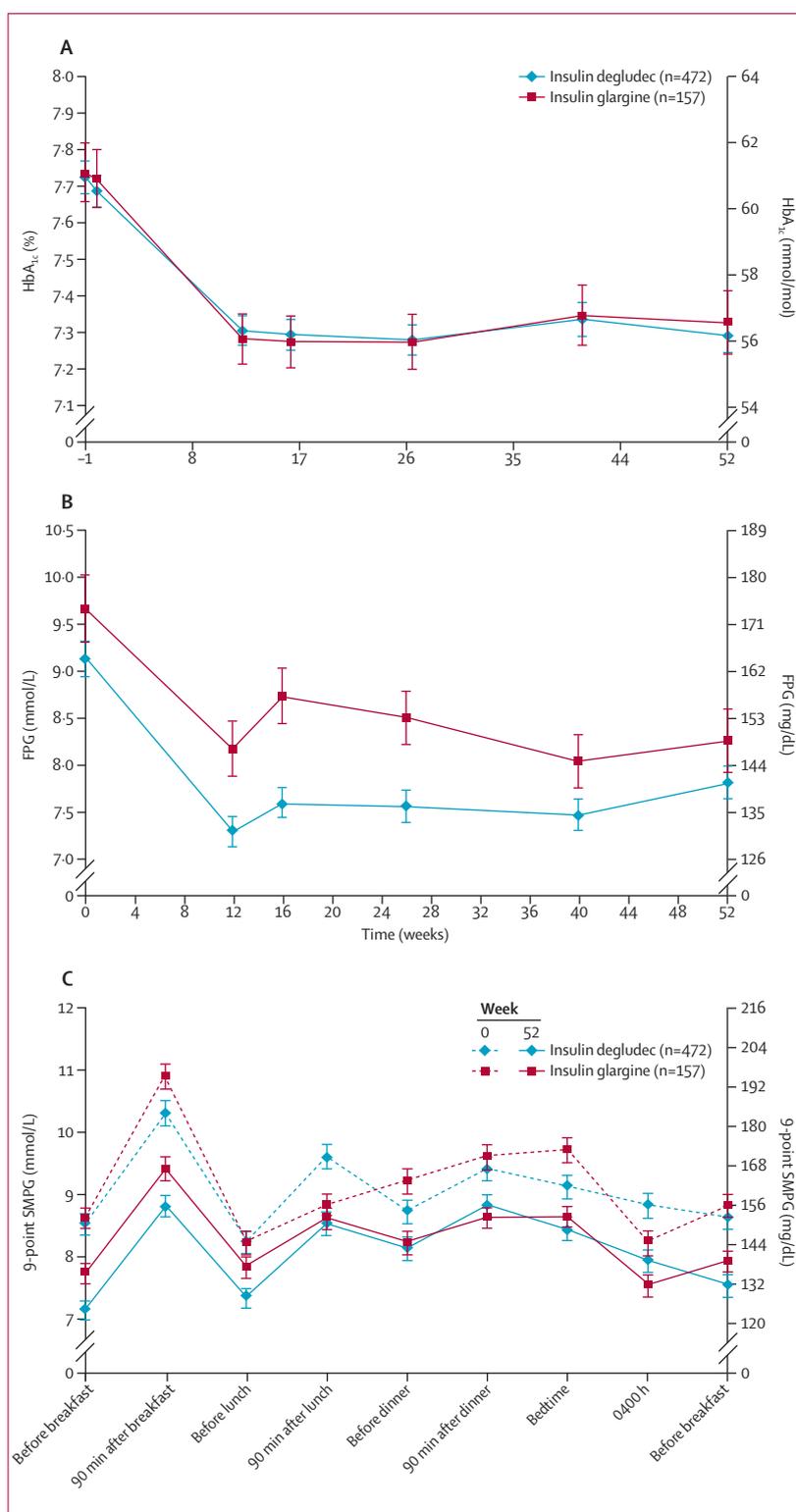


Figure 2: Glycaemic efficacy in the insulin degludec and insulin glargine groups (A) HbA_{1c}. (B) FPG. (C) 9-point SMPG at baseline and end of treatment. Data are mean (SE), reported for all randomly assigned participants (full-analysis set). Error bars represent SE. Last observation carried forward approach was used for imputing postbaseline missing data. FPG=fasting plasma glucose. HbA_{1c}=glycated haemoglobin. SMPG=self-measured fasting plasma glucose.

	Insulin degludec (U/kg; n=470)	Insulin glargine (U/kg; n=154)	Mean ratio* of insulin degludec to insulin glargine	Estimated treatment ratio† of insulin degludec to insulin glargine (95% CI)	p value
Basal insulin (degludec or glargine)					
Pretrial	0.37 (0.01)	0.36 (0.01)
Week 1	0.35 (0.01)	0.33 (0.01)
Week 52	0.35 (0.01)	0.39 (0.02)	0.91	0.86 (0.81–0.92)	<0.0001
Bolus insulin aspart (at mealtimes)					
Week 1	0.36 (0.01)	0.38 (0.01)
Week 52	0.40 (0.01)	0.44 (0.02)	0.90	0.90 (0.83–0.98)	0.016
Total insulin (basal + bolus)					
Week 1	0.72 (0.01)	0.71 (0.02)
Week 52	0.75 (0.02)	0.82 (0.03)	0.91	0.89 (0.84–0.93)	<0.0001

Data are mean (SE), unless otherwise indicated, for all participants exposed to treatment who contributed to analyses. Missing values at week 52 were imputed with the last observation carried forward approach. *Calculated as the ratio of mean doses of insulin degludec to insulin glargine at last treatment visit. †Estimated by use of ANOVA of log-transformed dose value (U/kg) at week 52 with treatment, antidiabetic therapy at screening, sex, and region as fixed factors, and age and week 1 dose as covariates.

Table 2: Daily insulin dose in the insulin degludec and insulin glargine groups

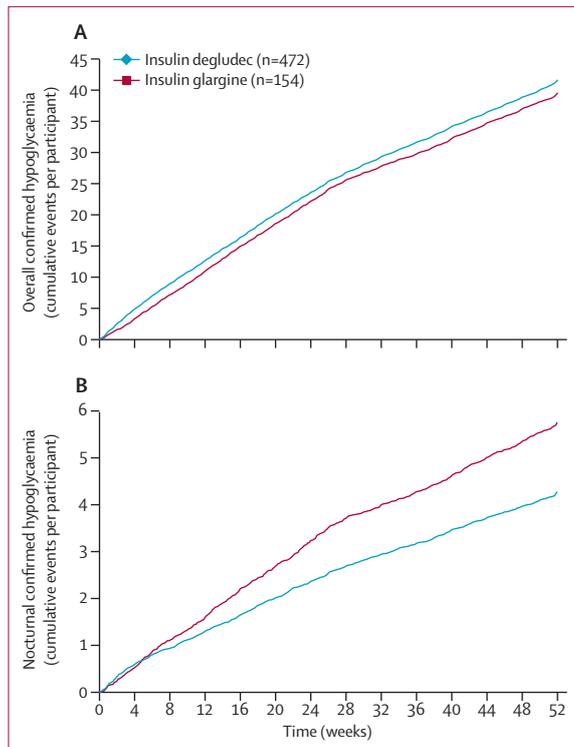


Figure 3: Overall confirmed (A) and nocturnal confirmed (B) hypoglycaemic episodes

Data are for all exposed participants (safety-analysis set). Insulin exposure period was from first day of treatment to no later than 7 days after the last day of treatment.

glargine and insulin aspart by the investigator. Two fatal myocardial infarctions were reported in the insulin degludec group and were not causally related to treatment—

one occurred after 79 days of treatment in a 67-year-old man whose medical history included diabetes, hypertension, and cardiovascular disease, and the other death occurred after 138 days of treatment in a 60-year-old man whose medical history included diabetes and obesity.

The median concentration of antibodies specific to insulin degludec was zero during the trial and the concentration of antibodies cross-reacting between insulin degludec and human insulin stayed low during the trial (appendix p 27). No apparent association between the development of insulin-degludec-specific antibodies or cross-reacting antibodies and HbA_{1c} or insulin dose was noted (data not shown).

No differences were noted in physical examination findings, vital signs, electrocardiography, fundoscopy, and laboratory measurements. No significant differences were seen in HRQoL assessments with the 36-item short form health (SF-36) survey (version 2; appendix p 28).

Discussion

Reduction in HbA_{1c} concentration from baseline with insulin degludec and insulin glargine was similar, thus establishing non-inferiority of insulin degludec to insulin glargine in improving long-term glycaemic control in type 1 diabetes. Further evidence of improved glycaemic control with both insulins was the reduction in FPG and SMPG. Mean SMPG before breakfast was significantly lower with insulin degludec than with insulin glargine; reduction in laboratory-reported FPG tended to be greater with insulin degludec than with insulin glargine, though the difference was not significant.

The before-breakfast titration target of 3.9 mmol/L to less than 5.0 mmol/L is lower than targets described in other intensive basal-bolus therapy trials in patients with type 1 diabetes—eg, prandial SMPG target of 3.9–6.7 mmol/L in the DCCT study.² The flat and stable pharmacokinetic profile of insulin degludec has the potential to lower hypoglycaemic risk.^{14,16} Therefore, an ambitious titration target was thought to be appropriate. Furthermore, the ultimate decision about the choice of insulin dose was made at the investigators' discretion.

Though glycaemic control was similar, participants treated with insulin degludec were using less basal, bolus, and total insulin at the end of the study than were those treated with insulin glargine. This difference might be attributable to a requirement for higher doses of insulin glargine to achieve adequate 24 h coverage when used once daily.

The similarity between rates of overall confirmed hypoglycaemia with insulin degludec and glargine (42.5 and 40.2 episodes per PYE) is supported by the finding that only 11% of all confirmed hypoglycaemic episodes were nocturnal; thus, the overall confirmed hypoglycaemia rate was mainly attributable to daytime episodes, probably related mainly to insulin aspart.

Nocturnal hypoglycaemia is more likely than are diurnal episodes to indicate hypoglycaemic risk attributed

	Insulin degludec (n=472)			Insulin glargine (n=154)			Estimated rate ratio of insulin degludec:insulin glargine (95% CI)	p value
	Participants	Hypoglycaemic episodes*	Rate per PYE	Participants	Hypoglycaemic episodes*	Rate per PYE		
Severe hypoglycaemia	58 (12%)	90	0.21	16 (10%)	23	0.16	1.38 (0.72-2.64)	0.34
Overall confirmed hypoglycaemia	451 (96%)	18 389	42.54	147 (95%)	5796	40.18	1.07 (0.89-1.28)	0.48
Diurnal confirmed hypoglycaemia	444 (94%)	15 928	36.09	145 (94%)	4831	32.82	1.11 (0.91-1.34)	0.30
Nocturnal confirmed hypoglycaemia	341 (72%)	1905	4.41	114 (74%)	845	5.86	0.75 (0.59-0.96)	0.021

Data are number or number (%), unless otherwise indicated. Interpretation of the number of participants and episodes must take into consideration the 3:1 (insulin degludec to insulin glargine) randomisation. PYE=patient-year of exposure. *Occurring on or after the first day of exposure to treatment and no later than 7 days after the last day of treatment with insulin degludec or insulin glargine.

Table 3: Hypoglycaemic episodes in the insulin degludec and insulin glargine groups

	Insulin degludec (n=472)			Insulin glargine (n=154)		
	Participants	Events	Event rate per 100 PYE	Participants	Events	Event rate per 100 PYE
Adverse events	397 (84%)	1895	438	128 (83%)	623	432
Serious adverse events	49 (10%)	59	14	17 (11%)	23	16
Severity						
Severe	75 (16%)	107	25	24 (16%)	34	24
Moderate	201 (43%)	502	116	60 (39%)	159	110
Mild	356 (75%)	1286	297	118 (77%)	430	298
Adverse events possibly or probably related to basal insulin	102 (22%)	161	37	26 (17%)	34	24
Injection-site reactions	13 (3%)	17	4	8 (5%)	11	8

Data are number or number (%), unless otherwise indicated. The complete list of adverse events is provided in the appendix p 15. Information about causality to the trial product were missing for eight events. PYE=patient-years of exposure.

Table 4: Summary of adverse events

to basal insulin since it largely eliminates the confounding effects of bolus doses. Notably, rates of nocturnal hypoglycaemia were 25% lower with insulin degludec, as found in a previous phase 2 trial.¹⁵ These results could be explained partly by differences in the pharmacokinetic profiles of the two insulins: insulin degludec has a longer half-life and exposure to this insulin is evenly distributed (about 50:50) in the first and second 12 h periods after once-daily dosing, whereas roughly 60% of exposure to insulin glargine occurs in the first 12 h after once-daily dosing.¹⁴ This uneven distribution could underlie the finding that the timing of administration of insulin glargine can affect nocturnal hypoglycaemia, such that more nocturnal hypoglycaemia occurs after evening or bedtime administration than after morning dosing.²² Although the timing of insulin glargine dosing was not recorded in our study, investigators were free to prescribe glargine at any time of day as per prescribing information and 70% of participants were using insulin glargine before joining the trial. By contrast, insulin degludec could be administered only with the evening meal.

The limitations of this trial are similar to those of any open-label trial; there is an underlying risk of reporting

bias or greater caution for adjustment of doses of the new drug insulin degludec. However, the delivery devices for the two basal insulins were different, preventing masking of treatments. Furthermore, unavailability of placebo-filled devices precluded a double-dummy design, although such a design would have been unethical in patients with type 1 diabetes. As mentioned previously, the time of insulin glargine administration was not systematically recorded, so we could not investigate whether it affected the risk of nocturnal hypoglycaemia. Although uniform titration of bolus doses at the multinational sites was desirable, this challenging goal was unlikely to have been achieved.

The rate of hypoglycaemia with insulin degludec, relative to insulin glargine, in the maintenance phase was lower than that estimated for the entire treatment duration of 52 weeks (rate ratios 1.02 vs 1.07 for overall confirmed hypoglycaemia and 0.73 vs 0.75 for nocturnal confirmed hypoglycaemia). This difference might be partly attributable to tighter glycaemic control in the maintenance period. The lower day-to-day variability of action of insulin degludec¹⁶ possibly underlies the finding of the lower rate of nocturnal hypoglycaemia coupled with the better

glycaemic control in the maintenance phase. An alternative explanation is that differences in the starting dose of basal insulin in patients treated with pretrial doses of twice-daily basal insulin, with the total daily basal dose being switched 1:1 for insulin degludec in the trial, and recommended to be reduced by 20–30% for insulin glargine (according to its prescribing information), led to more hypoglycaemia with insulin degludec in the initial weeks of treatment. Therefore, a dose reduction might be advisable for insulin degludec, especially when switching patients previously using twice-daily basal insulin whose glycaemic parameters are close to target.

Nevertheless, risk of nocturnal hypoglycaemic episodes is a major concern for patients with diabetes. Nocturnal hypoglycaemia impairs sleep quality and next-day wellbeing, resulting in decreased work productivity,^{5,10} and can contribute to a reduced awareness of hypoglycaemia.²³ Thus, reduced nocturnal hypoglycaemia could be thought of as a useful clinical advance (panel). In a clinical setting, the adverse symptoms of hypoglycaemia

and the unfavourable effect of hypoglycaemia on quality of life can result in both patients and physicians avoiding stringent glycaemic control to prevent recurrence. Although this approach might be appropriate for patients with a history of severe hypoglycaemia, advanced microvascular or macrovascular complications, and extensive comorbidities, a reduction in hypoglycaemic risk, particularly nocturnal, might encourage more reasonable efforts to strive for stricter glycaemic control in patients with a short duration of diabetes, long life expectancy, and no significant cardiovascular disease. The benefits of improved glycaemic control in controlling long-term microvascular and macrovascular complications might be easier to emphasise in light of the reduced risk of nocturnal hypoglycaemia.

Rates of severe hypoglycaemia in intensive therapy trials in patients with type 1 diabetes mellitus have decreased in recent years. The rates of severe hypoglycaemia reported in this study were roughly three to four times lower than the rate (0.62 episodes per PYE) reported in DCCT.² Importantly, rates of severe hypoglycaemia are much higher in everyday practice than in clinical trials, as shown by the 20 times higher rate reported in a prospective observational study based in secondary care centres for diabetes in the UK.²⁴ This difference is partly because patients with recurrent episodes are usually excluded from trials, but also because those in trials receive close supervision and are treated according to protocol. Whether reductions in hypoglycaemia reported in clinical trials translate into benefits in clinical practice remains to be seen.

Insulin degludec provides similar glycaemic control to insulin glargine with a lower rate of nocturnal hypoglycaemia, suggesting a potential role for insulin degludec in helping patients with type 1 diabetes to reach and maintain tight glucose targets.

Contributors

SH, BB, SG, JB, MF, AP, LM, MM, ER, and DR-J helped obtain data, interpret the data, and prepare the final report. SH and BB prepared the first draft of the report. AMOF was the International Medical Director, was responsible for medical oversight during the study, and helped interpret the data and prepare the final report. HP was the trial statistician and helped to analyse and interpret data and prepare the final report.

Conflicts of interest

BB has received payment for consultancy, research support, and speakers' bureau and medical advisory board participation from Novo Nordisk, Eli Lilly, and Sanofi. SG has received grants through the University of Colorado for clinical research from Novo Nordisk, Sanofi, Merck, Eli Lilly, Cebix, MannKind, Medtronic MiniMed, and DexCom; he has also received honoraria for giving lectures from DexCom, Merck, and Sanofi; neither he nor any of his family members have stocks in any of the pharmaceutical or device companies. JB is an investigator, consultant, or both, without any direct financial benefit to him under contracts between his employer and Amylin Pharmaceutical, Andromeda, Bayhill Therapeutics, Biodel, Boehringer Ingelheim, Bristol-Myers Squibb, Catabasis, Diartis, Elcelyx, Eli Lilly, Exsulim, GI Dynamics, Halozyme, Hoffman-La Roche, Johnson and Johnson, Lexicon, LipoScience, Medtronic MiniMed, Merck, Metabolon, Novan, Novo Nordisk Pharmaceuticals, Osiris Therapeutics, Orexigen, Pfizer, Sanofi, TolereX, Transition Therapeutics, and TransPharma. MF has served on advisory boards and has received honoraria for lectures from Novo Nordisk,

Panel: Research in context

Systematic review

We searched PubMed, Embase, and abstracts presented at the 2011 American Diabetes Association for articles with terms “insulin therapy”, “insulin treatment”, “insulin regimen”, “insulin analogue”, “detemir”, “NPH”, “glargine”, “degludec”, and “hypoglycaemia”. We did not set any criteria for assessment of quality.

Interpretation

Glycaemic control is essential to reduce the risk of long-term complications that are associated with diabetes. Hypoglycaemia, associated with insulin treatment is a major barrier to the achievement and maintenance of good glycaemic control. Even non-severe hypoglycaemia adversely affects the management of diabetes and work productivity.⁵ Subcutaneous systemic insulin delivery is a major contributor to hypoglycaemic risk because it cannot mimic the normal physiology of insulin secretion. Insulin analogues have been developed to provide improved physiological coverage of insulin needs. The development of the insulin analogues, such as insulin glargine and insulin detemir, is an important advance in the treatment of diabetes because these insulins are associated with a reduced risk of nocturnal hypoglycaemia compared with neutral protamine Hagedorn insulin. However, these insulins do not reliably provide 24 h basal insulin replacement in all patients, which is particularly important in type 1 diabetes because the patients have no endogenous insulin reserves. Insulin degludec is an ultra-longacting insulin that is in clinical development; it has a flat, stable pharmacokinetic profile, and a duration of action that is longer than 42 h.¹⁴ In this treat-to-target phase 3 study in patients with type 1 diabetes, insulin degludec reduced the risk of nocturnal hypoglycaemia by 25% compared with insulin glargine. However, the rate of daytime hypoglycaemia, which was probably much affected by mealtime insulin, was similar in the insulin degludec and insulin glargine groups. Thus, further studies are needed to establish improved titration guidelines about how best to combine insulin degludec with mealtime insulin in patients with type 1 diabetes. The clinical significance of the potential advantage of insulin degludec in basal-bolus therapy for type 1 diabetes is in agreement with results of a phase 3 basal-bolus study in patients with longstanding type 2 diabetes in whom insulin degludec achieved glycaemic control that was similar to insulin glargine, with reduced overall and nocturnal hypoglycaemia. Thus, insulin degludec potentially provides an improved basal insulin (as shown by lower rates of hypoglycaemia) that should be used in the management of diabetes.

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References

- Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005; **353**: 2643–53.
- The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; **329**: 977–86.
- American Diabetes Association. Standards of medical care in diabetes—2011. *Diabetes Care* 2011; **34**: S11–S61.
- Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009; **32**: 193–203.
- Brod M, Christensen T, Thomsen TL, et al. The impact of non-severe hypoglycemic events on work productivity and diabetes management. *Value Health* 2011; **14**: 665–71.
- Davis RE, Morrissey M, Peters JR, et al. Impact of hypoglycaemia on quality of life and productivity in type 1 and type 2 diabetes. *Curr Med Res Opin* 2005; **21**: 1477–83.
- Frier BM. How hypoglycaemia can affect the life of a person with diabetes. *Diabetes Metab Res Rev* 2008; **24**: 87–92.
- Smith CB, Choudhary P, Pernet A, et al. Hypoglycemia unawareness is associated with reduced adherence to therapeutic decisions in patients with type 1 diabetes: evidence from a clinical audit. *Diabetes Care* 2009; **32**: 1196–98.
- Chico A, Vidal-Rios P, Subira M, et al. The continuous glucose monitoring system is useful for detecting unrecognized hypoglycemia in patients with type 1 and type 2 diabetes but is not better than frequent capillary glucose measurements for improving metabolic control. *Diabetes Care* 2003; **26**: 1153–57.
- King P, Kong MF, Parkin H, et al. Well-being, cerebral function, and physical fatigue after nocturnal hypoglycemia in IDDM. *Diabetes Care* 1998; **21**: 341–45.
- Little S, Shaw J, Home P. Hypoglycemia rates with basal insulin analogs. *Diabetes Technol Ther* 2011; **13** (suppl 1): S53–S64.
- DeVries JH, Natrass M, Pieber TR. Refining basal insulin therapy: what have we learned in the age of analogues? *Diabetes Metab Res Rev* 2007; **23**: 441–54.
- Jonassen I, Havelund S, Ribell U, et al. Insulin degludec is a new generation ultra-long acting basal insulin with a unique mechanism of protraction based on multi-hexamer formation. *Diabetes* 2010; **59** (suppl 1): A11.
- Heise T, Hovelmann U, Nosek L, Botchner S, Granhall C, Hahr H. Insulin degludec has a two-fold longer half-life and a more consistent pharmacokinetic profile than insulin glargine. *Diabetes* 2011; **60** (suppl 1A): LB11.
- Birkeland KI, Home PD, Wendisch U, et al. Insulin degludec in type 1 diabetes: a randomized controlled trial of a new-generation ultra-long-acting insulin compared with insulin glargine. *Diabetes Care* 2011; **34**: 661–65.
- Heise T, Hermanski L, Nosek L, et al. The pharmacodynamic variability of insulin degludec is consistently lower than insulin glargine over 24 hours at steady state. *Diabetes* 2011; **60** (suppl 1): A263.
- World Medical Association. Declaration of Helsinki. Ethical principles for medical research involving human subjects. *J Indian Med Assoc* 2009; **107**: 403–05.
- ICH Harmonised Tripartite Guideline: guideline for good clinical practice. *J Postgrad Med* 2001; **47**: 199–203.
- US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Guidance for industry: diabetes mellitus: developing drugs and therapeutic biologics for treatment and prevention. 2008. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071624.pdf> (accessed March 19, 2010).
- Lindholm A, Jensen LB, Home PD, et al. Immune responses to insulin aspart and biphasic insulin aspart in people with type 1 and type 2 diabetes. *Diabetes Care* 2002; **25**: 876–82.
- Mire-Sluis AR, Barrett YC, Devanarayan V, et al. Recommendations for the design and optimization of immunoassays used in the detection of host antibodies against biotechnology products. *J Immunol Methods* 2004; **289**: 1–16.
- Hamann A, Matthaes S, Rosak C, et al. A randomized clinical trial comparing breakfast, dinner, or bedtime administration of insulin glargine in patients with type 1 diabetes. *Diabetes Care* 2003; **26**: 1738–44.
- Veneman T, Mitrakou A, Mokan M, et al. Induction of hypoglycemia unawareness by asymptomatic nocturnal hypoglycemia. *Diabetes* 1993; **42**: 1233–37.
- UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia* 2007; **50**: 1140–47.