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 [HbA1c] ≤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 HbA1c 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, HbA1c 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 HbA1c of less than 7% (<53 mmol/mol). Rates of overall confirmed hypoglycaemia (plasma glucose <3·1 mmol/L or severe) were similar in the insulin degludec and insulin glargine groups (42·5 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.12 The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) recommend a glycated haemoglobin (HbA1c) target of less than 7% (<53 mmol/mol), without substantial hypoglycaemia.23 A history of hypoglycaemia and the fear of further episodes, particularly at night, can lead to poor adherence to treatment and compromise glycaemic control.14 Nocturnal hypoglycaemia is associated with poor quality of sleep, decreased sense of wellbeing, fatigue, and reduced productivity.1,2,5,20

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.19 However, neither insulin reliably provides 24 h basal insulin replacement on all
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. 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. Pharmacokinetic data show that insulin degludec has a flat, stable profile at steady state and a terminal half-life of more than 24 h, which is twice that of insulin glargine, and a duration of action greater than 40 h. 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, perhaps because in pharmacodynamic studies the day-to-day variability with insulin degludec was four times lower.

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 HbA1c 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 Helsinki and Good Clinical Practice Guidelines. 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, 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, Bagsvaerd, 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. 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 prettrial 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.
Safety variables were adverse events, hypoglycaemic episodes, insulin dose, bodyweight, injection-site reactions, abnormal findings related to physical examination, vital signs, fundoscopy, 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 assistance (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.

**Statistical analysis**

The primary objective was to confirm the non-inferiority of insulin degludec to insulin glargine in reduction in HbA1c from baseline after 52 weeks of treatment. 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 HbA1c 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 HbA1c. 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 (HbA1c, FPG, SMPG, 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. 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 HbA1c, 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 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...
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 HbA1c, 7.7% [59 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 HbA1c, 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 HbA1c 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 HbA1c 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 (95% CI −1·03 to 0·36; 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

<table>
<thead>
<tr>
<th>Basal insulin type at screening</th>
<th>Insulin degludec</th>
<th>Insulin glargine</th>
</tr>
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<tbody>
<tr>
<td>Glargine</td>
<td>334 (71%)</td>
<td>108 (69%)</td>
</tr>
<tr>
<td>Detemr</td>
<td>87 (18%)</td>
<td>34 (22%)</td>
</tr>
<tr>
<td>Neutral protamine Hagedorn</td>
<td>37 (8%)</td>
<td>12 (8%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (&lt;1%)</td>
<td>-</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Bolus insulin at screening</th>
<th>Insulin degludec</th>
<th>Insulin glargine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspart</td>
<td>244 (52%)</td>
<td>81 (52%)</td>
</tr>
<tr>
<td>Lispro</td>
<td>183 (39%)</td>
<td>59 (38%)</td>
</tr>
<tr>
<td>Other</td>
<td>45 (10%)</td>
<td>17 (11%)</td>
</tr>
</tbody>
</table>
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).

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 degludec.
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 HbA1c 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 HbA1c 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 3.9–6.7 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, preprandial SMPG target of 3.9–6.7 mmol/L in the DCCT study. The flat and stable pharmacokinetic profile of insulin degludec has the potential to lower hypoglycaemic risk. 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

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

<table>
<thead>
<tr>
<th>Basal insulin (degludec or glargine)</th>
<th>Pretrial</th>
<th>Week 1</th>
<th>Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean dose (U/kg) (n=470)</td>
<td>0.35 (0.01)</td>
<td>0.36 (0.01)</td>
<td>0.35 (0.01)</td>
</tr>
<tr>
<td>Estimated treatment ratio† of insulin degludec to insulin glargine (95% CI)</td>
<td>0.91</td>
<td>0.86 (0.81–0.92)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bolus insulin aspart (at mealtimes)</th>
<th>Week 1</th>
<th>Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean dose (U/kg) (n=470)</td>
<td>0.35 (0.01)</td>
<td>0.39 (0.02)</td>
</tr>
<tr>
<td>Estimated treatment ratio† of insulin degludec to insulin glargine (95% CI)</td>
<td>0.91</td>
<td>0.86 (0.81–0.92)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total insulin (basal + bolus)</th>
<th>Week 1</th>
<th>Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean dose (U/kg) (n=470)</td>
<td>0.72 (0.01)</td>
<td>0.75 (0.02)</td>
</tr>
<tr>
<td>Estimated treatment ratio† of insulin degludec to insulin glargine (95% CI)</td>
<td>0.91</td>
<td>0.89 (0.84–0.93)</td>
</tr>
</tbody>
</table>

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 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.

### 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.
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 timing 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 degludec possibly underlies the finding of the lower rate of nocturnal hypoglycaemia coupled with the better

<table>
<thead>
<tr>
<th>Hypoglycaemic episodes</th>
<th>Rate per PYE</th>
<th>Estimated rate ratio of insulin degludec:insulin glargine (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal All hypoglycaemia</td>
<td>438</td>
<td>128 (83%)</td>
<td>623</td>
</tr>
<tr>
<td>Severe</td>
<td>438</td>
<td>17 (11%)</td>
<td>23</td>
</tr>
<tr>
<td>Moderate</td>
<td>116</td>
<td>24 (16%)</td>
<td>34</td>
</tr>
<tr>
<td>Mild</td>
<td>297</td>
<td>60 (39%)</td>
<td>159</td>
</tr>
<tr>
<td>Adverse events possibly or probably related to basal insulin</td>
<td>37</td>
<td>26 (17%)</td>
<td>34</td>
</tr>
<tr>
<td>Injection-site reactions</td>
<td>4</td>
<td>8 (5%)</td>
<td>11</td>
</tr>
</tbody>
</table>

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.
glycaemic control in the maintenance phase. An alternative explanation is that differences in the starting dose of basal insulin in patients treated with prettrial 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, and can contribute to a reduced awareness of hypoglycaemia. 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. 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. 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.

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. 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. 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.

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, Cechx, MannKind, Medtronic MiniMed, and DesCom; he has also received honoraria for giving lectures from DesCom, 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, Catalysis, DiaBets, Elyxys, Eli Lilly, Exsulin, GI Dynamics, Hakeynmey, Hoffman-La Roche, Johnson and Johnson, Lexicon, LipoScience, Medtronic MiniMed, Merck, Metabolon, Novan, Novo Nordisk Pharmaceuticals, Ostis Therapeutics, Orexigen, Pfizer, Sanofi, Tolerex, Transition Therapeutics, and TransPharma. MF has served on advisory boards and has received honoraria for lectures from Novo Nordisk.
Eli Lilly, and Sanofi, and the Diabetes Department at Glasgow Royal Infirmary has received payment for participation in studies from Novo Nordisk, Eli Lilly, and Sanofi. SH has received payment for lecture fees, consultancy, and research support from Amylin, AstraZeneca, Eli Lilly, Johnson and Johnson, Mannkind, Novo Nordisk, Sanofi, and Takeda. LM has received honoraria as consultant or speaker from AstraZeneca, Boehringer Ingelheim, Bristol-Meyers Squibb, Eli Lilly, Merck Sharpe and Dohme, Novo Nordisk, and Roche Pharma; neither he nor his family members hold stocks in pharmaceutical or device companies. MM has received research funds from Novo Nordisk, Sanofi, Novartis, Merck, and Servier, and has received honoraria as consultant or speaker from Novo Nordisk, Sanofi, Eli Lilly, Servier, Merck, and Abbott. AP has received research support and has acted as consultant and speaker for Novo Nordisk and Sanofi; neither she nor any of her family members own stocks in any of the pharmaceutical or device companies. ER has received honoraria as consultant or speaker from Novo Nordisk, Eli Lilly, Sanofi, Roche Diagnostics, Medtronic, Abbott Diabetes Care, Lifescan, Animas, Novartis, Merck Sharp and Dohme, A Menzatti Diagnostics, and GlaxoSmithKline. DR-J has received research grants from Novo Nordisk, Takeda, Pfizer, Boehringer Ingelheim, Eli Lilly, and Merck Serono; he has also received honoraria for giving lectures from Novo Nordisk, Eli Lilly, Takeda, Merck Sharp and Dohme, and GlaxoSmithKline. AMOF and HP are employees and shareholders of Novo Nordisk. The authors did not receive any payment for writing or contributing to the report.

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