Short Report: Treatment

Insulin degludec improves glycaemic control with lower nocturnal hypoglycaemia risk than insulin glargine in basal–bolus treatment with mealtime insulin aspart in Type 1 diabetes (BEGIN® Basal–Bolus Type 1): 2-year results of a randomized clinical trial

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Abstract

Aims The goal of this study was to compare the long-term safety and efficacy of the basal insulin analogue, insulin degludec with insulin glargine (both with insulin aspart) in Type 1 diabetes, over a 2-year time period.

Methods This open-label trial comprised a 1-year main trial and a 1-year extension. Patients were randomized to once-daily insulin degludec or insulin glargine and titrated to pre-breakfast plasma glucose values of 3.9–4.9 mmol/l.

Results The rate of nocturnal confirmed hypoglycaemia was 25% lower with insulin degludec than with insulin glargine (P = 0.02). Rates of confirmed hypoglycaemia, severe hypoglycaemia and adverse events, and reductions in glycated haemoglobin and fasting plasma glucose were similar between groups. Despite achieving similar glycaemic control, insulin degludec-treated patients used 12% less basal and 9% less total daily insulin than did insulin glargine-treated patients (P < 0.01).

Conclusions Long-term basal therapy using insulin degludec in Type 1 diabetes required lower doses and was associated with a 25% lower risk for nocturnal hypoglycaemia than insulin glargine.

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Introduction

New, long-acting basal insulin analogues with more predictable pharmacodynamics may lower the risk of hypoglycaemia over that of the current marketed insulin analogues insulin glargine and insulin detemir [1]. Insulin degludec is a basal insulin analogue (approved thus far in Europe, Japan, Mexico and other regions) with a half-life of 24 h. In contrast, insulin glargine has a half-life of 12 h and a greater glucose-lowering effect during the first 12 h after injection compared with the subsequent 12 h. The flat insulin-action curve and 4-fold lower variability of insulin degludec [2] result in similar efficacy, but lower risk of hypoglycaemia with insulin degludec than with insulin glargine [3]. Risk reduction in nocturnal hypoglycaemia with insulin degludec was demonstrated in a 52-week, randomized, head-to-head comparison (BEGIN® Basal–Bolus Type 1; hereafter, BEGIN) of once-daily insulin degludec and insulin glargine, both with mealtime insulin aspart, in Type 1 diabetes [4]. This paper describes a 52-week extension to the BEGIN main trial and assesses the long-term safety and efficacy of insulin degludec in the same population.
What’s new?

- Insulin degludec is the first basal insulin analogue with an ultra-long duration of action for the treatment of Type 1 and Type 2 diabetes mellitus.
- The pharmacokinetic and pharmacodynamic profile of insulin degludec results in similar efficacy but reduces the risk of nocturnal hypoglycaemia compared with currently marketed basal insulins.
- This multi-centre, multinational, 2-year study reaffirms the long-term safety and efficacy of insulin degludec in patients with Type 1 diabetes in a basal–bolus regimen with insulin aspart.

Patients and methods

In the main trial, 629 patients who had previously used long-term basal–bolus therapy were randomized (3:1) to once-daily insulin degludec (472 subjects) or insulin glargine (157) for 52 weeks, with basal insulin titrated to pre-breakfast plasma glucose values of 3.9–4.9 mmol/l. Insulin aspart was taken before each meal and titrated to achieve preprandial and bedtime plasma glucose values of 3.9–4.9 mmol/l. Patients entering the extension continued their therapy for another 52 weeks with the same titration target. Data are reported from baseline of the main trial to the end of the extension trial (week 104).

The same assessments were performed during the main and extension trials [4]. Safety variables were assessed descriptively based on the safety analysis set (patients exposed to trial products) and extension trial set (patients entering the extension) and included adverse events, hypoglycaemic episodes, insulin dose, body weight and standard safety parameters. Confirmed hypoglycaemic episodes included those with a plasma glucose value of < 3.1 mmol/l or severe episodes necessitating assistance. Hypoglycaemic episodes occurring from 00.01 to 05.59 h (both included) were classified as nocturnal. Rate ratios of hypoglycaemic episodes were estimated based on the full analysis set (randomized patients) by use of a negative binomial regression model with treatment, anti-diabetic therapy at screening, sex and region as fixed factors, and age as covariate, for all treatment-emergent episodes.

Key efficacy endpoints included change in HbA1c, fasting plasma glucose and 9-point self-measured plasma glucose profiles, with treatment differences from baseline to week 104 estimated by analysis of covariance (ANCOVA) performed based on the full analysis set, with treatment, anti-diabetic treatment at screening, sex and region as fixed factors, and age and baseline values as covariates. The analysis of change in HbA1c was repeated based on the extension trial set.

In-person or phone study visits were performed weekly in the first 26 weeks and every 2 weeks thereafter. Missing values were imputed using the last-observation-carried-forward approach. Alpha level was 0.05.

Results

Baseline characteristics were similar between groups [4] (see Supporting Information, Table S1, for baseline characteristics of the full analysis set and extension trial set). A similar proportion of subjects in both groups entered the extension [74% (351/472) insulin degludec; 75% (118/157) insulin glargine] and completed it [94% (330/351) insulin degludec; 96% (113/118) insulin glargine]. A small proportion of subjects withdrew because of adverse events [< 1% (3/351) insulin degludec; 2% (2/118) insulin glargine], hypoglycaemia [< 1% (1/351) insulin degludec; 0% (0/118) insulin glargine] or ineffective therapy [< 1% (2/351) insulin degludec; 0% (0/118) insulin glargine]. Other reasons for withdrawal were generally unrelated to safety or efficacy (see also Supporting Information, Fig. S1).

Safety

A similar proportion of subjects in both groups reported adverse events [87.5% (413/472) insulin degludec; 89.0% (137/154) insulin glargine], most of which were mild. A smaller proportion of subjects in the insulin degludec group than in the insulin glargine group reported injection-site reactions [3.0% (14/472) insulin degludec; 5.8% (9/154) insulin glargine] or serious adverse events [15.0% (71/472) insulin degludec; 18.8% (29/154) insulin glargine]. Serious adverse events reported in the extension trial set over the course of the 2-year trial are summarized by system organ class in the Supporting Information (Table S2). Body weight increase was modest (2.1 kg insulin degludec; 2.0 kg insulin glargine; not statistically significant).

The rate of nocturnal confirmed hypoglycaemia was significantly lower with insulin degludec [3.9 vs. 5.3 episodes/patient-year of exposure; estimated rate ratio (insulin degludec/insulin glargine): 0.75 [95% CI 0.59–0.95]; P = 0.02; Fig. 1a]. The rates of overall confirmed hypoglycaemia were similar in both groups (Fig. 1b). During the maintenance period [defined post hoc as the period of optimal basal insulin dosage and stable glycaemic control (i.e. from week 16 onwards)], the rate ratio was 0.98 (0.80–1.20) (NS) for confirmed hypoglycaemia and 0.73 (0.56–0.94) (P = 0.02) for nocturnal confirmed hypoglycaemia.

Eight major adverse cardiovascular events were reported by eight (1.7%) subjects treated with insulin degludec and two events by two (1.3%) subjects treated with insulin glargine. Four deaths occurred in the insulin degludec group.
(two myocardial infarction events; one sudden death; one ventricular tachycardia event) and three in the insulin glargine group (one sudden death; one ventricular arrhythmia event; one metastatic gall bladder cancer event). Interpretation of safety results should take into account the 3:1 randomization scheme of the trial.

**Efficacy**

After 104 weeks, the observed mean HbA1c was reduced by 0.27%-points and 0.24%-points to 57 and 58 mmol/mol (7.4 and 7.5%) (full analysis set) and by 0.31%-points and 0.24%-points to 56 and 58 mmol/mol (7.3 and 7.5%)

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**FIGURE 1** Safety and efficacy of long-term use of insulin degludec measured in terms of (a) nocturnal confirmed hypoglycaemia over the treatment period (safety analysis set), (b) overall confirmed hypoglycaemia over the treatment period (safety analysis set), (c) HbA1c values over time (full analysis set), (d) 9-point self-measured plasma glucose values over time (full analysis set) and (e) insulin dose over time (safety analysis set). The efficacy parameters are presented as the mean (se; represented by error bars). The full analysis set consisted of all randomly assigned participants. The safety analysis set consisted of all participants who had been exposed to the trial drug. Missing data were imputed using the last-observation-carried-forward approach.

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(extension trial set) with insulin degludec and insulin glargine, respectively (Fig. 1c). The estimated mean treatment difference of -0.04% points was not statistically significant [-0.17 to 0.09]; full analysis set).

Fasting plasma glucose and 9-point self-measured plasma glucose were reduced to a similar extent in both groups (NS) (Fig. 1d). At the end of 104 weeks, the daily insulin dose was significantly lower in the insulin degludec group: the dose ratios (insulin degludec/insulin glargine) were 0.88 (0.82–0.94) (P < 0.001) for basal insulin, 0.94 (0.86–1.03) (P = 0.18) for bolus insulin and 0.91 (0.86–0.97) (P = 0.002) for total insulin. Mean daily doses of insulin degludec increased slightly, but generally remained stable, throughout treatment. Insulin glargine doses increased substantially in the first 5 weeks and continued to increase slightly thereafter (Fig. 1e). The mean daily insulin aspart dose increased during the first 12 weeks of the main trial in both groups and remained stable thereafter. Similar to week 1, the basal-to-bolus split of total daily insulin dose at the end of the trial was 48/52% for the insulin degludec group and 47/53% for the insulin glargine group.

### Discussion

This 2-year study demonstrated that patients with Type 1 diabetes who continued insulin degludec therapy experienced similar long-term fasting plasma glucose and HbA1c to that of patients treated with insulin glargine, but with lower risk of nocturnal hypoglycaemia. These results are consistent with those of the BEGIN main trial and others involving insulin degludec and insulin glargine in Type 1 diabetes [3–5]. The lower risk of nocturnal hypoglycaemia observed with insulin degludec may be attributable to its ultra-long action profile and less variable glucose-lowering effect [2,6]. The open-label design may have biased safety reporting. Although extension studies may have biased outcomes, because those experiencing more benefit are more likely to enter the extension, few subjects withdrew after 1 year and similar proportions in both groups entered the extension.

The hypoglycaemia curves showed increased differences in the risk of nocturnal hypoglycaemia between insulins over time, which suggests that the risk reduction with insulin degludec is a sustained effect and may improve as patients learn to titrate this new insulin optimally. The similarity in overall confirmed hypoglycaemic episodes between groups suggests that the hypoglycaemia benefit of insulin degludec was not observed during the day, when bolus insulin exerts a greater effect—a finding that is also consistent with the main trial results [4]. The results of this extension trial support the long-term safety of insulin degludec and its potential as a useful advance in basal insulin therapy in diabetes, where hypoglycaemia and the fear of hypoglycaemia are barriers to achieving euglycaemia.

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### Competing interests

BWB’s employer has received research and grant support from Novo Nordisk, Eli Lilly and Co., Sanoﬁ, MannKind and Biodel. He has also received honoraria for speaking engagements and consulting fees from Novo Nordisk, Eli Lilly and Co. and Sanoﬁ.

JBB is an investigator and/or consultant without any direct financial benefit to him under contracts between his employer and the following companies: Amylin Pharmaceuticals Inc., Andromeda, AstraZeneca, Bayhill Therapeutics, Biodel, Boehringer-Ingelheim, Bristol-Myers Squibb, Catalysis, Cebix, Diartis, Eli Lilly and Co., Exsulin, GI Dynamics, Halozyme, Hoffman-LaRoche, Johnson and Johnson, Lexicon, LipoScience, Medtronic MiniMed, Merck, Metabolon, Novan, Novo Nordisk, Osiris Therapeutics, Orexigen, Pfizer, Sanoﬁ, Tolerex, Transition Therapeutics, TransPharma and Verva Pharmaceuticals.

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MM has participated in advisory boards for Eli Lilly and Co., Merck, Novo Nordisk, Roche, Sanoﬁ and Servier, and has received scientific support from Novo Nordisk. He has also given lectures for Abbott, Merck, Novo Nordisk, Sanoﬁ and Servier, and participated in clinical trials for Eli Lilly and Co., Merck, Novartis, Novo Nordisk, Sanoﬁ and Servier.

LM has received honoraria as a consultant or speaker from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly and Co., Merck Sharpe and Dohme, Novo Nordisk and Roche Pharma. Neither he nor his family members hold stocks in pharmaceutical or device companies.

ER has acted as consultant for A. Menarini Diagnostics, Abbott, Cellnovo, DexCom Inc., Eli Lilly and Co., Johnson and Johnson (Animas, LifeScan), Medtronic, Novartis, Novo Nordisk, Roche Diagnostics and Sanoﬁ. He has also received honoraria for speaking at the University of Colorado Denver for clinical research from Eli Lilly and Co., Merck, Novo Nordisk, Sanoﬁ and Servier.

CTH is employed by Novo Nordisk A/S and owns shares in the company.
AR is employed by Novo Nordisk A/S and owns shares in the company.

SRH has served on advisory panels for Eli Lilly and Co., Novo Nordisk, Johnson and Johnson and Takeda. He has acted as consultant for Eli Lilly and Co., Novo Nordisk and Sanoﬁ, and has served on speakers’ bureaus for Eli Lilly and Co., Novo Nordisk and MSD. He has also served on a trial steering committee for Takeda.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Subject disposition.
Table S1. Demographic and baseline characteristics.
Table S2. Serious adverse events by system organ class—extension trial set.
Appendix S1. List of investigators in the BEGIN® Basal–Bolus Type 1 trial.