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Insulin degludec improves long-term glycaemic control similarly to insulin glargine but with fewer hypoglycaemic episodes in patients with advanced type 2 diabetes on basal–bolus insulin therapy

RESEARCH LETTER

The aim of the present study was to compare the long-term safety and efficacy of insulin degludec with those of insulin glargine in patients with advanced type 2 diabetes (T2D) over 78 weeks (the 52-week main trial and a 26-week extension). Patients were randomized to once-daily insulin degludec or insulin glargine, with mealtime insulin aspart ± metformin ± pioglitazone, and titrated to pre-breakfast plasma glucose values of 3.9–4.9 mmol/l (70–88 mg/dl). After 78 weeks, the overall rate of hypoglycaemia was 24% lower ($p = 0.011$) and the rate of nocturnal hypoglycaemia was 31% lower ($p = 0.016$) with insulin degludec in the extension trial set, while both groups of patients achieved similar glycaemic control. Rates of adverse events and total insulin doses were similar for both groups in the safety analysis set. During 18 months of treatment, insulin degludec + mealtime insulin aspart ± oral antidiabetic drugs in patients with T2D improves glycaemic control similarly, but confers lower risks of overall and nocturnal hypoglycaemia than with insulin glargine treatment.
Keywords: glycaemic control, hypoglycaemia, insulin degludec, type 2 diabetes

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Introduction

Insulin degludec is a new basal insulin with an ultra-long duration of action [1,2]. In a 52-week, randomized, treat-to-target trial (the BEGIN Basal-Bolus Type 2 trial) in patients with advanced type 2 diabetes (T2D) previously treated with insulin, insulin degludec improved glycaemic control similarly to insulin glargine but with a significantly lower rate of overall and nocturnal hypoglycaemia when administered once daily with mealtime insulin aspart with or without the use of oral antidiabetic drugs [3]. The 26-week extension of this study, described in the present paper, was designed to investigate the longer-term safety and efficacy of insulin degludec compared with insulin glargine in the same population.

Methods

In the BEGIN Basal–Bolus Type 2 trial, 1006 adult patients with advanced T2D previously treated with insulin were randomized to treatment with once-daily insulin degludec or insulin glargine in a 3 : 1 ratio [3]. Basal insulin was administered in combination with mealtime insulin aspart with or without metformin, pioglitazone or both. Patients who completed the main trial and provided informed consent entered the 26-week extension trial. As re-randomization was not performed, the patients continued the treatment allocated to them in the main trial (Figure S1).

The treatment algorithms, safety and efficacy assessments and statistical methodologies used in the extension were the same as those used in the main trial [3]. Insulin degludec was administered with the main evening meal; insulin glargine was administered at the same time every day (according to the label) as chosen by the patient and investigator. Basal insulin was titrated to target a pre-breakfast plasma glucose concentration of 3.9–4.9 mmol/l (70–88 mg/dl) based on the mean of pre-breakfast self-measured plasma glucose values from the preceding three consecutive days.

The primary objective of the extension trial was to investigate the long-term safety and tolerability of insulin degludec. Safety data over 78 weeks were evaluated for the safety analysis set, comprising patients exposed to treatment after randomization (including those who did not enter the extension). Hypoglycaemia, glycated haemoglobin (HbA1c) and fasting plasma glucose were analysed in the extension trial population, comprising patients who completed the main trial and were exposed to treatment during the extension. Hypoglycaemia, and HbA1c and fasting plasma glucose levels were also evaluated for the full analysis set, comprising all randomized patients excluding 14 from one closed trial site.

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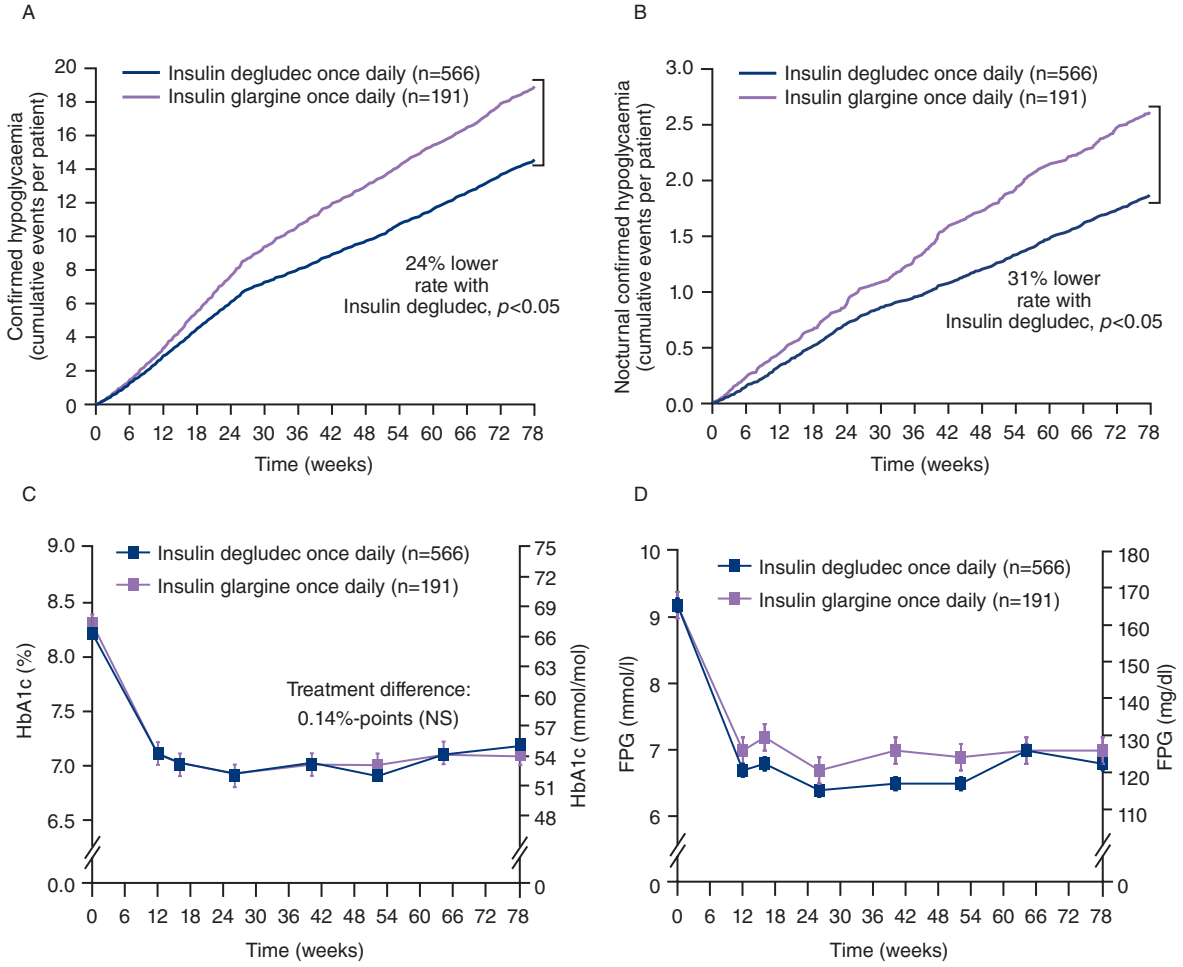

Figure 1. Confirmed hypoglycaemia and glycaemic control in patients with type 2 diabetes in the extension trial set over 78 weeks of treatment with insulin degludec once daily or insulin glargine once daily. (A) Episodes of overall confirmed hypoglycaemia [defined as episodes with plasma glucose <3.1 mmol/l (56 mg/dl) or severe episodes requiring assistance] during the treatment period. (B) Episodes of nocturnal confirmed hypoglycaemia (occurring between 00:01 and 05:59 hours) during the treatment period. (C) HbA1c values over time. (D) Fasting plasma glucose levels (as measured by the central laboratory) over time. The extension trial set comprised patients who had completed the main trial and were exposed to treatment during the extension period. HbA1c and fasting plasma glucose data are presented as means (error bars represent standard errors). FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; NS, non-significant.

Statistical analyses included calculation of estimated mean treatment differences (or ratios) with two-sided 95% confidence intervals (CIs) and p values for two-sided testing with an α level (type I error probability) of 0.05.

The trial was registered at clinicaltrials.gov under the number NCT01193322.

Results

Similar proportions of patients in the insulin degludec and insulin glargine groups completed the 52-week main trial (82%, 618/755 patients and 84%, 211/251 patients, respectively), continued treatment in the extension (75%, 566/755 patients and 76%, 191/251 patients, respectively) and completed the 26-week extension (71%, 539/755 patients and 73%, 183/251 patients, respectively). Similar proportions of patients withdrew from the insulin degludec (3.6%) and insulin glargine (3.2%) groups during the extension (Table S1). The baseline characteristics of the two treatment groups were well matched for both the extension trial set (Table S2) and the full analysis set [3].

Safety

The mean daily basal insulin dose was 0.76 and 0.71 U/kg in the insulin degludec and insulin glargine groups, respectively, after 78 weeks; the mean daily bolus insulin doses were: 0.21 and 0.23 U/kg at breakfast, 0.25 and 0.26 U/kg at lunch, and 0.29 and 0.30 U/kg at the main evening meal (safety analysis set), respectively. The mean total daily insulin dose was 1.5 U/kg in both treatment groups.

The estimated rate of overall confirmed hypoglycaemia [episodes with plasma glucose <3.1 mmol/l (56 mg/dl) or severe episodes requiring assistance] in the extension trial set was 24% lower with insulin degludec than insulin glargine

Table 1. Hypoglycaemic episodes in the insulin degludec and insulin glargine groups.

Extension trial set, entire trial period	Insulin degludec once daily (n = 566)*				Insulin glargine once daily (n = 191)*				Estimated rate ratio; insulin degludec/ insulin glargine (95% CI)†	p
	Patients		Episodes	Rate episodes/PYE	Patients		Episodes	Rate episodes/PYE		
	n	%			n	%				
Overall confirmed	487	86.0	8300	9.84	165	86.4	3631	12.76	0.76 (0.62; 0.94)	0.011
Nocturnal confirmed	255	45.1	1068	1.27	111	58.1	505	1.77	0.69 (0.51; 0.93)	0.016
Severe	30	5.3	40	0.05	14	7.3	17	0.06	0.66 (0.31; 1.37)	NS
Safety analysis set, entire trial period	**Insulin degludec once daily (n = 753)*‡**				**Insulin glargine once daily (n = 251)***				**Estimated rate ratio; insulin degludec/ insulin glargine (95% CI)§**	**p**
	Patients		**Episodes**	**Rate episodes/PYE**	**Patients**		**Episodes**	**Rate episodes/PYE**		
	n	**%**			**n**	**%**				
Overall confirmed	617	81.9	9847	10.39	208	82.9	4098	12.71	0.85 (0.70; 1.02)	NS
Nocturnal confirmed	316	42.0	1266	1.34	132	52.6	567	1.76	0.76 (0.58; 0.996)	0.047
Severe	39	5.2	51	0.05	16	6.4	19	0.06	0.83 (0.43; 1.61)	NS

Hypoglycaemic episodes (overall confirmed, nocturnal confirmed and severe), 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, are included for the extension trial set (comprising patients who completed the main trial and were exposed to treatment during the extension) and safety analysis set (comprising all patients who were exposed to at least one dose of treatment after they were randomized, including those who did not enter the extension). CI, confidence interval; PYE, patient-years of exposure; NS, non-significant.

*Patients were randomized 3 : 1 to insulin degludec or insulin glargine treatment in the main trial.

†Statistical analysis based on the extension trial set.

‡Two patients who were randomized in the main trial were withdrawn before being exposed to treatment.

§Statistical analysis based on the full analysis set (insulin degludec once daily, n = 744; insulin glargine once daily, n = 248), comprising all randomized patients, excluding 14 patients from one closed trial site.

[estimated rate ratio (ERR) insulin degludec/insulin glargine 0.76 (95% CI 0.62; 0.94), p = 0.011 (Figure 1A and Table 1)]. In the full analysis set population, the rates of overall confirmed hypoglycaemia were not significantly different between the insulin degludec and insulin glargine groups [ERR: 0.85 (95% CI 0.70; 1.02); non-significant].

The estimated rate of nocturnal confirmed hypoglycaemia (00:01–05:59 hours) was 31% lower with insulin degludec than with insulin glargine [ERR 0.69 (95% CI 0.51; 0.93); p = 0.016] in the extension trial set population (Figure 1B and Table 1). Lower rates of nocturnal hypoglycaemia were also observed with insulin degludec in the full analysis set [ERR 0.76 (95% CI 0.58; 1.00); p = 0.047].

The estimated rates of severe hypoglycaemia were low and not significantly different between insulin degludec and insulin glargine in both the extension trial set [ERR 0.66 (95% CI 0.31; 1.37) non-significant] and the full analysis set populations [ERR 0.83 (95% CI 0.43; 1.61); non-significant (Table 1)].

Similar proportions of patients reported adverse events in the insulin degludec (84%) and insulin glargine (83%) groups (safety analysis set population; Table S3). Patients in both groups experienced similar rates of adverse events [four events/patient-years of exposure (PYE)] and serious adverse events (0.2 events/PYE). The rates of major adverse cardiovascular events for insulin degludec and insulin glargine were low (0.03 and 0.02 events/PYE, respectively); see Table S3 for the rates of individual components of major adverse cardiovascular events (acute coronary syndrome, stroke and cardiovascular death). Additional data regarding cardiovascular risk factors (blood pressure, heart rate and lipid concentrations) are provided in Table S4. The rates of injection-site reactions for insulin degludec and insulin glargine were 0.05 and 0.02 events/PYE, respectively. Most of the adverse events in each group were mild. The most frequently reported serious adverse events in both groups were hypoglycaemia (0.01 event/PYE) and coronary artery disease (0.01 event/PYE; Tables S5 and S6).

Ten deaths (eight in the insulin degludec group, two in the insulin glargine group) were reported in the main trial [3] (note that patients were randomized 3 : 1 to insulin degludec or insulin glargine treatment). Three additional deaths were reported in the insulin degludec group during the extension (attributed to brain-stem haemorrhage, metastasis to the central nervous system from a bronchial carcinoma and unknown cause). Investigators judged that none of these three deaths were related to trial products.

Body weight increased by 4.0 kg with insulin degludec and by 4.4 kg with insulin glargine [estimated treatment difference (ETD) between insulin degludec and insulin glargine: −0.34 kg (95% CI −1.05; 0.38); non-significant].

Efficacy

In the extension trial population, the mean HbA1c value decreased from 8.2% at baseline to 7.2% after 78 weeks of treatment with insulin degludec and from 8.3 to 7.1% with insulin glargine (Figure 1C); the ETD between insulin degludec and insulin glargine was 0.14 percentage points (95% CI −0.01; 0.30); non-significant. In the full analysis set population, the mean HbA1c value decreased from 8.3% at baseline to 7.3% with insulin degludec and from 8.4 to 7.2% with insulin glargine. The ETD was 0.16 percentage points (95% CI 0.02; 0.30; p = 0.022); the upper bound of the CI was below the

non-inferiority margin of 0.4% that was defined in the main trial.

The central laboratory-measured fasting plasma glucose level decreased by 2.4 mmol/l (43 mg/dl) after 78 weeks of treatment with insulin degludec and by 2.2 mmol/l (40 mg/dl) after treatment with insulin glargine in the extension trial set population (Figure 1D); the ETD was −0.19 (95% CI −0.59; 0.21) mmol/l [−3.4 (95% CI −10.6; 3.8) mg/dl; non-significant]. Similar results were obtained in the full analysis set population.

Conclusions

This 18-month study showed that patients with advanced T2D who continued insulin degludec therapy experienced long-term improvements in glycaemic control similar to those experienced by patients treated with insulin glargine at similar doses, but with lower risks of overall and nocturnal confirmed hypoglycaemia. Furthermore, the rate of adverse events and serious adverse events in the insulin degludec group were similar to those in the insulin glargine group; thus, the benefits with regard to hypoglycaemia observed in the main trial are supported by the results of the extension trial as the duration of treatment with insulin degludec is increased. One patient needs to be treated for 4 months with insulin degludec to avoid one confirmed hypoglycaemic episode compared with treatment with insulin glargine. Two patients need to be treated for 1 year with insulin degludec to avoid one nocturnal confirmed hypoglycaemic episode compared with insulin glargine.The lower rate of hypoglycaemia with insulin degludec may be connected to the lower day-to-day variability in its glucose-lowering effect [4,5].

The hypoglycaemic benefit with insulin degludec versus insulin glargine was emphasized recently by a meta-analysis of nocturnal hypoglycaemia in insulin degludec trials using different definitions for hypoglycaemia [6]. The same benefits regarding nocturnal hypoglycaemia with insulin degludec were observed using the definition of plasma glucose <3.9 mmol/l (70 mg/dl) with symptoms or the definition used in this study.

As hypoglycaemia and fear of hypoglycaemia are barriers to treatment optimization, adherence and the goal of reaching normoglycaemia, the reduced risk of hypoglycaemia with insulin degludec compared with insulin glargine during 18 months of treatment may provide an improved clinical profile for patients with T2D.

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An abstract including some of the study data was accepted for presentation as a poster at the International Diabetes Federation World Diabetes Congress in 2013: 'Insulin degludec improves long-term glycaemic control with less hypoglycaemia than insulin glargine in advanced type 2 diabetes' by Garber et al.

Conflict of Interest

P. H. has served on advisory boards for Novo Nordisk, Merck and Sanofi. A. B. K. has received research support from Sanofi, Novo Nordisk and Eli Lilly, fees for lecturing from Sanofi, Novo Nordisk and Eli Lilly, and served on advisory boards for Sanofi, Novo Nordisk and Eli Lilly. S. D.-P. has received fees for lecturing from Boehringer Ingelheim, Novartis, and Sanofi-Aventis, served on advisory boards for Astra Zeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Lilly, GlaxoSmithKline, Intarcia, Janssen, Merck, Novartis, Novo Nordisk, Roche, Sanofi-Aventis and Takeda; and received research support from Bristol-Myers Squibb, Merck, Novartis, Novo Nordisk, Sanofi-Aventis and Takeda. S. S. has received fees for lecturing from Novo Nordisk, Eli Lilly and Novartis; served on advisory boards for Novartis, Bristol-Myers Squibb, Janssen, Boehringer Ingelheim, Sanofi-Aventis and Novo Nordisk; and has received research support from Novo Nordisk, Boehringer Ingelheim and Abbott. M. K. B. has served on advisory boards for Novo Nordisk, Astra Zeneca and Merck Sharp & Dohme. He is also Vice President of the Turkish Endocrine Society. M. M.-T. has received fees for lecturing from Lilly-Boehringer, Novartis, Novo Nordisk and Amgen, has served on advisory boards for Amgen and Novo Nordisk and has received research support from Janssen, Roche, Novo Nordisk, Amgen and Lilly-Boehringer. J. R. has served on advisory boards and received honoraria or consulting fees from Sanofi, Novo Nordisk, Eli Lilly, GlaxoSmithKline, Takeda, Merck, Daiichi Sankyo, Janssen, Novartis, Boehringer Ingelheim, MannKind, Halozyme, Intarcia and Lexicon, and has received grants/research support from Merck, Pfizer, Sanofi, Novo Nordisk, Roche, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Takeda, Novartis, AstraZeneca, Amylin, Janssen, Daiichi Sankyo, MannKind, Boehringer Ingelheim,

Intarcia and Lexicon. C. T. M. is an employee and shareholder of Novo Nordisk. M. N. is an employee of Novo Nordisk. A. J. G. has served as a consultant and/or on advisory boards for Novo Nordisk, Merck, Salix, Tethys, Halozyme, Vivus, Janssen, Viking Therapeutics, Lexicon, GSK and Bayer, and is on speakers' bureaux for Merck, Salix, Novo Nordisk, Janssen, Vivus, Eisai and Takeda. He also serves on the Board of Directors of the American Association of Clinical Endocrinologists (AACE).

All authors (P. H., A. B. K., S. D.-P., S. S., M. K. B., M. M.-T., J. R., C. T. H., M. N., A. J. G.) were involved in critical analysis and interpretation of the data, drafting/critically revising the article and shared in the final responsibility for the content of the manuscript and the decision to submit it for publication.

Supporting Information

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

Figure S1. Trial design and inclusion criteria.

Table S1. Patients meeting withdrawal criteria in extension study.

Table S2. Demographic and baseline characteristics.

Table S3. Summary of adverse events.

Table S4. Summary of blood pressure, heart rate and lipid concentrations at baseline and week 78.

Table S5. Serious adverse events occurring at frequency ≥1%.

Table S6. Serious adverse events possibly/probably related to the trial product.

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