Insulin degludec in Japanese patients with type 1 diabetes mellitus: A randomized controlled trial

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ABSTRACT

Introduction: Insulin degludec is an ultra-long-acting insulin with a flat time-action profile and duration of action >42 h. Data from several studies have shown insulin degludec to have a favorable therapeutic profile in type 1 and type 2 diabetes.

Materials and Methods: This was a 6-week, parallel-group, randomized controlled trial carried out in 65 Japanese patients with type 1 diabetes, previously treated with mealtime insulin aspart and either insulin glargine or neutral protamine Hagedorn insulin. Patients were randomized to receive either insulin degludec or insulin detemir, each once daily and at the same unit dose as pretrial basal insulin. During the trial, basal insulin was titrated according to a prespecified algorithm in order to achieve a fasting plasma glucose target of 80–109 mg/dL.

Results: No severe hypoglycemia occurred; there was no significant difference in confirmed hypoglycemia rates with insulin degludec and insulin detemir (rate ratio degludec/detemir 0.78; 95% confidence interval 0.45–1.34). The rate of nocturnal confirmed hypoglycemia was 69% lower with insulin degludec than with insulin detemir (rate ratio 0.31; 95% confidence interval 0.13–0.78). Final fasting plasma glucose levels were similar (insulin degludec 147 mg/dL, insulin detemir 136 mg/dL), despite differing baseline fasting plasma glucose levels.

Conclusions: In conclusion, no concerns relating to hypoglycemia or general safety were observed when initiating insulin degludec in Japanese patients with type 1 diabetes at the same unit dose as previous basal insulin. This trial was registered with ClinicalTrials.gov (no. NCT00841087). (J Diabetes Invest, doi: 10.1111/j.2040-1124.2012.00240.x, 2013)

KEY WORDS: Insulin analogs and derivatives, Long-acting insulin, Type 1 diabetes mellitus

INTRODUCTION

Insulin is central to treatment of diabetes mellitus and is essential therapy in type 1 diabetes. In the 90 years since its first human use, insulin therapy has undergone many refinements, including the introduction of analogs with improved pharmacokinetic properties, and the advancement of insulin delivery devices and regimens. Despite these advances, however, many people with type 1 diabetes, in Japan and elsewhere, remain in suboptimal glycemic control[1–3]. In part, this is a reflection of the pharmacological limitations of exogenous insulin therapy – intensifying control is generally accompanied by an increased risk of hypoglycemia. Additionally, a psychosocial burden is associated with insulin therapy, especially where multiple daily injections are required, which might make patients less willing to intensify therapy in search of improved glycemic control.

A key factor underlying these problems is the inability of current basal insulins to provide continuous and reproducible action over a 24-h period from a single subcutaneous injection[4,5]. Currently available basal insulin products do not cover basal insulin requirements over a period of 24 h in all patients and might thus need to be administered twice daily[6–9]. Furthermore, there is considerable within-patient variation in metabolic effect of basal insulins after subcutaneous injection[10,11]. Together with their pronounced peak effect some hours after injection, this results in an inconsistent blood glucose-lowering effect during the day and from day to day, confounding attempts to intensify therapy and optimize glycemic control[5,11].

Insulin degludec has been designed to allow the formation of multi-hexamers after subcutaneous injection. As the insulin multi-hexamers are too large for transcapillary absorption, this results in formation of a soluble depot from which insulin monomers are steadily released and enter into the circulation over a prolonged period of time. Insulin degludec has a terminal half-life of 25.4 h, and a duration of action that exceeds 42 h in Caucasian patients with type 1 diabetes[12,13]. Euglycemic clamp data in people with type 1 diabetes show insulin degludec to have up to fourfold lower within-subject pharmacodynamic variability than insulin glargine under steady-state conditions[14]. Recent data from a 1-year study in type 1 diabetes

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show that insulin degludec in a basal-bolus regimen improved glycemic control with a 25% lower risk of nocturnal hypoglycemia compared with insulin glargine[15]. Similarly, a 16-week study found a 28% lower risk of overall confirmed hypoglycemia and a 58% lower risk of nocturnal hypoglycemia with insulin degludec compared with insulin glargine[16]. To date, no studies have evaluated insulin degludec in Japanese patients; we report here an exploratory, randomized, controlled trial of insulin degludec in Japanese patients with type 1 diabetes, designed to assess the safety of this insulin in a basal-bolus regimen.

MATERIALS AND METHODS

The trial was a 6-week, multicenter, randomized, parallel-group, open-label study in Japanese patients with type 1 diabetes. Eight centers in Japan participated in the study, which took place between January 2009 and May 2009, and was carried out in accordance with the Declaration of Helsinki, and the Ministry of Health and Welfare Ordinance on Good Clinical Practice[17,18]; local institutional review boards approved the protocol and all participants gave informed consent. The primary objective of the study was to investigate the safety (with emphasis on hypoglycemia) of insulin degludec in a basal-bolus regimen, with measures of short-term glucose control as secondary end-points.

National Glycohemoglobin Standardization Program values are used throughout the present report[19]. Participants included in the trial were patients with type 1 diabetes aged $\geq$20 years with glycated hemoglobin (HbA_{1c}) level <10.4% and body mass index (BMI) <30.0 kg/m^2. Eligible participants had a known history of type 1 diabetes for at least 12 months, and had been treated for at least 12 weeks with a basal-bolus insulin regimen using insulin glargine or neutral protamine Hagedorn (NPH) insulin as the basal component and insulin aspart as the bolus component. The protocol excluded patients with clinically significant concomitant disease, impaired renal (serum creatinine $\geq$1.7 mg/dL) or hepatic (transaminases >2.5-fold the upper limit of normal range) function, non-stabilized proliferative retinopathy or maculopathy, or a history of recurrent severe hypoglycemia or hypoglycemia unawareness. Pregnant or breastfeeding women were also excluded.

Patients entering the study were randomized in a 1:1 ratio using an external registration center (patients were stratified by pretrial basal insulin treatment) to receive treatment with either insulin degludec or insulin detemir, each administered once daily at bedtime using the same starting unit dose as the pretrial basal insulin. All patients administered insulin aspart before meals three times a day, using the same unit doses as the pretrial period. All insulins were injected subcutaneously using NovoPen® 300 (Novo Nordisk A/S, Bagsværd, Denmark) for insulin degludec and FlexPen® (Novo Nordisk A/S) for insulin detemir and insulin aspart.

Treatment was continued for 6 weeks, during which time basal insulin dose was adjusted at weekly telephone/site visits based on pre-breakfast self-monitored blood glucose (SMBG) value, aiming at a fasting plasma glucose (FPG) level of 80–109 mg/dL and using a 1-unit increase if FPG was 110–129 mg/dL, 2 units if FPG was 130–159 mg/dL, or 3 units if FPG was $\geq$160 mg/dL. FPG values $\leq$79 mg/dL resulted in a 1-unit decrease. Bolus insulin doses were adjusted at the investigator's discretion.

FPG was measured (by central laboratory, SRL Inc., Tokyo, Japan) at baseline, 2 and 6 weeks, and a 9-point SMBG profile (before and 120 min after each meal, at bedtime, 03.00 hours, and pre-breakfast the next day) was recorded at baseline and at end of trial. SMBG was measured by patients using supplied glucose meters: Glutest AceR®, Glutest PRO R® (both Sanwa-Kagaku, Nagoya, Japan), Glucocard Diameter or Glucocard Diameter α (both Arkray KDK Corp, Kyoto, Japan).

The principal safety assessment was hypoglycemia, categorized as severe (requiring the assistance of another person), confirmed (associated with a measured plasma glucose $\leq$55 mg/dL) and symptoms-only (symptomatic with measured plasma glucose $\geq$56 mg/dL or without plasma glucose measurement). Nocturnal hypoglycemia was defined as an event occurring after 23.00 hours and before 06.00 hours. Other safety assessments included hematology and biochemistry, carried out by central laboratory (SRL Inc.), and electrocardiogram, bodyweight and blood pressure.

Safety evaluations were based on data from all randomized patients who had received at least one dose of trial products. The number of hypoglycemic episodes was analyzed using a generalized linear model based on a negative binomial distribution, and including treatment group and pretrial insulin treatment (insulin glargine or NPH insulin) as fixed factors and observation time as an offset variable. Efficacy end-points were based on data from all randomized and exposed patients with at least one post-baseline value for either FPG or 9-point SMBG profile. Efficacy end-points (changes from baseline to 6 weeks) were analyzed using an analysis of variance model with treatment group and pretrial basal insulin as fixed factors, and baseline value as covariate. Sample size for this phase 2 study was not determined from statistical considerations.

RESULTS

A total of 66 patients were screened, of whom 65 were randomized and exposed to trial products (insulin degludec 33, insulin detemir 32). All of the exposed patients completed the trial (Figure 1).

The trial population consisted of 43 male (66%) and 22 female Japanese patients with type 1 diabetes, with a mean age of 44 years, a mean duration of diabetes of 12.5 years, a mean HbA_{1c} of 7.8% and a mean BMI of 22.9 kg/m^2 (Table 1). Most of the participants had concomitant illnesses, with retinopathy the most common complication (approximately 31%). The majority of participants in both groups (approximately 90% in each group) used insulin glargine before the start of the trial.

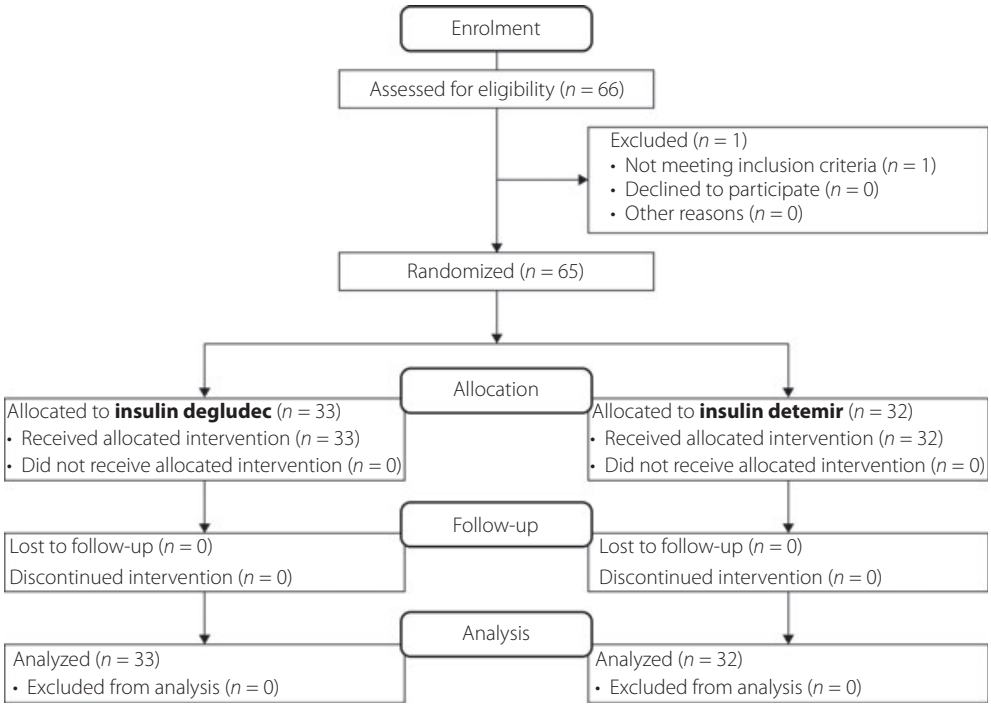

Figure 1 | Consolidated standards of reporting trials (CONSORT) flowchart.

Table 1 | Characteristics of trial participants

Item	Insulin degludec	Insulin detemir
Sex, *n* (%)*		
Male	24 (72.7)	19 (59.4)
Female	9 (27.3)	13 (40.6)
Age (years)*	45.5 (15.0)	43.2 (15.4)
Bodyweight (kg)*	64.52 (11.03)	62.50 (7.72)
BMI (kg/m^2)*	22.92 (2.49)	22.87 (2.50)
Duration of diabetes (years)*	13.23 (9.12)	11.75 (9.00)
HbA_{1c} (%)*	7.79 (0.86)	7.72 (0.86)
FPG at the central laboratory (mg/dL)†	181.8 (66.2)	141.8 (54.3)
PG before breakfast from 9-point SMBG profile (mg/dL)†	128.7 (75.5)	135.5 (74.1)
Basal insulin dose (U)*	15.7 (6.7)	16.2 (7.0)
Total daily insulin dose (U)*	47.5 (16.6)	49.0 (22.0)
Pretrial basal insulin treatment, *n* (%)*		
Insulin glargine	29 (87.9)	29 (90.6)
NPH insulin	4 (12.1)	3 (9.4)

Data are mean (SD) unless otherwise stated.
*Screening visit.
†Baseline visit.
BMI, body mass index; FPG, fasting plasma glucose; NPH, neutral protein Hagedorn; PG, plasma glucose; SMBG, self-monitored blood glucose.

Differences between groups at baseline were generally minor, apart from a 40-mg/dL higher FPG value in the insulin degludec group than in the insulin detemir group. This difference was not reflected in the before-breakfast SMBG values at baseline, which were similar (128.7 and 135.5 mg/dL, respectively).

During the study, mean basal and total daily insulin dose increased in the insulin degludec group from 15.7 to 18.0 units and from 47.5 to 49.2 units, respectively. There was little change in insulin doses in the insulin detemir group (basal 16.2 –16.5 units, total 49.0–48.7 units).

Hypoglycemia and Safety

No patient in the present study experienced severe hypoglycemia. There was no significant difference between insulin groups in the rate of confirmed hypoglycemic episodes [insulin degludec, 63 episodes/patient/year; insulin detemir, 81 episodes/patient/year; rate ratio 0.78, 95% confidence interval (CI) 0.45–1.34]. Non-severe hypoglycemia occurred in the majority of patients (insulin degludec 91%, insulin detemir 78%; Table 2).

Fewer patients experienced nocturnal confirmed hypoglycemia in the insulin degludec group than with insulin detemir (36 vs 47%; Table 2), with a significantly lower rate (insulin degludec five episodes/patient/year; insulin detemir 16 episodes/patient/year; rate ratio 0.31, 95% CI 0.13–0.78).

Differences in nocturnal hypoglycemia between groups, and the non-significant trend to lower overall hypoglycemia with insulin degludec, were evident throughout the trial with a consistent divergence of event curves (Figure 2). Evaluation of time

Table 2 | Frequency distribution and analyses of all (24 h) and nocturnal hypoglycemic episodes

	Insulin degludec			Insulin detemir		
	n (%)	No. of episodes	Rate	*n* (%)	No. of episodes	Rate
Exposed	33 (100.0)			32 (100.0)		
All hypoglycemic episodes	30 (90.9)	315	74.56	25 (78.1)	365	88.88
Severe (assistance required)	0 (0.0)	0	0.00	0 (0.0)	0	0.00
Confirmed non-severe (PG $\leq$ 55 mg/dL)	30 (90.9)	266	62.97	25 (78.1)	332	80.84
Symptoms only (PG > 55 mg/dL)	12 (36.4)	49	11.60	10 (31.3)	33	8.04
Nocturnal hypoglycemic episodes	12 (36.4)	25	5.92	17 (53.1)	74	18.02
Severe (assistance required)	0 (0.0)	0	0.00	0 (0.0)	0	0.00
Confirmed non-severe (PG $\leq$ 55 mg/dL)	12 (36.4)	21	4.97	15 (46.9)	65	15.83
Symptoms only (PG > 55 mg/dL)	4 (12.1)	4	0.95	6 (18.8)	9	2.19

	Rate ratio (95% CI) degludec/detemir
All hypoglycemic episodes	0.84 (0.49–1.44)
Severe (assistance required)	–
Confirmed non-severe (PG $\leq$ 55 mg/dL)	0.78 (0.45–1.34)
Symptoms only (PG > 55 mg/dL)	1.45 (0.46–4.57)
Nocturnal hypoglycemic episodes	0.33 (0.14–0.77)
Severe (assistance required)	–
Confirmed non-severe (PG $\leq$ 55 mg/dL)	0.31 (0.13–0.78)
Symptoms only (PG > 55 mg/dL)	0.43 (0.11–1.65)

PG, plasma glucose; CI, confidence interval; rate, number of episodes per year of exposure.

of onset of hypoglycemic episodes suggested that hypoglycemia was more frequent with insulin detemir than insulin degludec in the night-time and first part of the day, with a trend to higher incidence with insulin degludec than with insulin detemir in the later evening period (Figure 2).

Other safety measures were comparable between groups. No serious or severe adverse events were reported, and most adverse events were comparable between groups, mild and considered unlikely to be related to the trial product. No clinically relevant differences were observed in laboratory measurements, vital signs, bodyweight or electrocardiogram.

Glycemic Control

Observed reductions in FPG were numerically greater in the insulin degludec group (which had a higher baseline FPG level) than with insulin detemir (35.1 vs 6.1 mg/dL) and final levels were thus similar after 6 weeks (insulin degludec 146.7 mg/dL, insulin detemir 135.7 mg/dL). The estimated treatment difference (insulin degludec–insulin detemir) in change in FPG (adjusted by baseline) was 3.1 mg/dL (95% CI −25.7 to 31.9). However, because of the imbalance observed at baseline, the result should be interpreted with caution. Somewhat fewer patients reached the FPG target of 110 mg/dL (based on SMBG profile) with insulin degludec than with insulin detemir (52 and 69%, respectively).

The 9-point SMBG profiles showed differences between groups in the night-time and pre-breakfast periods (Figure 3). At the 03.00 hours time-point, estimated mean change in plasma glucose from baseline to 6 weeks was 54 mg/dL with insulin degludec and 6.4 mg/dL with insulin detemir [difference 47.5 mg/dL (95% CI 8.0–87.1)]. Before breakfast, mean changes were −6.1 mg/dL with insulin degludec and –39.6 mg/dL with insulin detemir [difference 33.5 mg/dL (95% CI 6.3–60.7)]. There was no significant difference between groups in changes in mean plasma glucose and mean postprandial increment from baseline to end of trial [difference in change, insulin degludec–insulin detemir; mean glucose 7.02 mg/dL (95% CI −12.15–26.19); postprandial glucose increment, −1.86 mg/dL (95% CI −25.31–21.60)].

DISCUSSION

In this exploratory phase 2 trial, we examined the safety of initiating the ultra-long-acting basal insulin degludec in Japanese patients with type 1 diabetes treated using a basal-bolus regimen with insulin aspart. This is the first report of the use of insulin degludec in Japanese patients.

In comparison with the basal insulin analog, detemir, we found that insulin degludec provided similar levels of glycemic control, but significantly lower (69%) risk of nocturnal hypoglycemia. Levels of overall hypoglycemia were not significantly different in the present 6-week trial, but cumulative event curves suggest a trend to a lower rate with insulin degludec than insulin detemir that could have reached statistical significance in a longer or larger trial.

The finding of a reduced risk of nocturnal hypoglycemia with insulin degludec in comparison with insulin detemir is

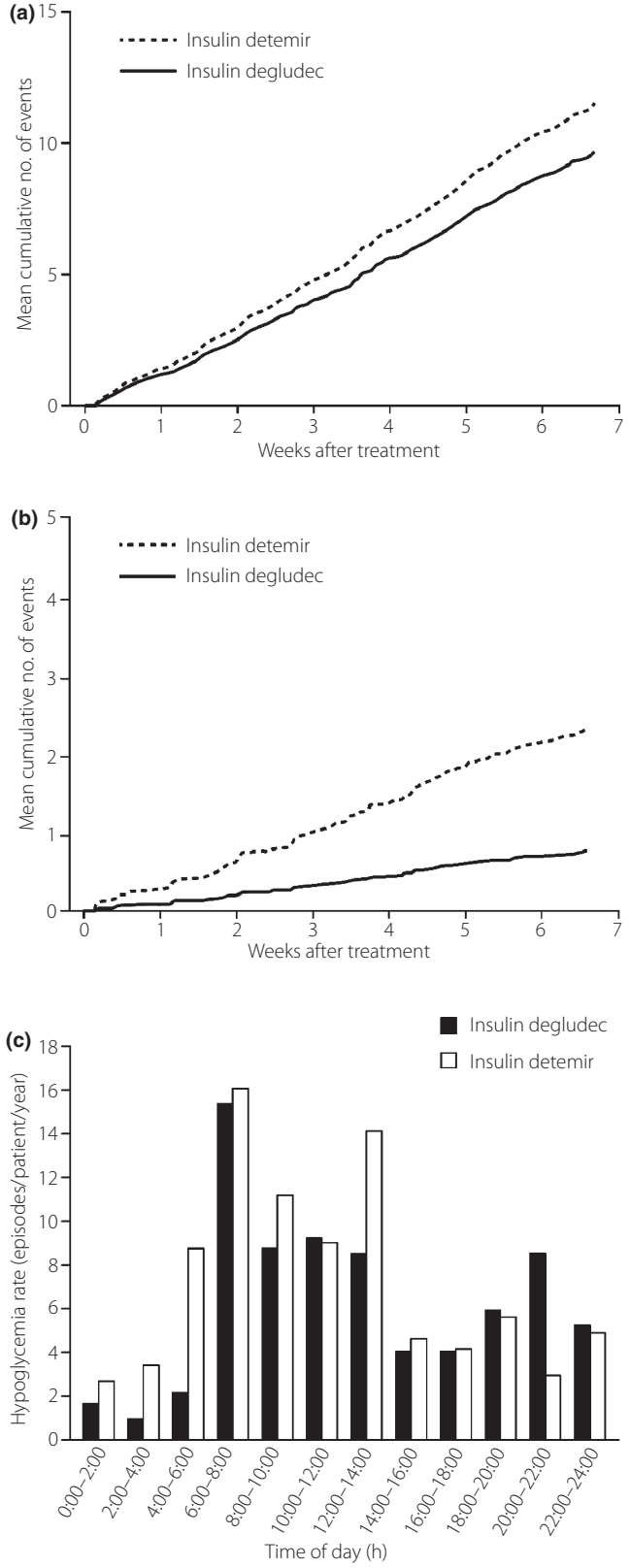

Figure 2 | Cumulative incidence of (a) overall (including severe, confirmed non-severe and symptoms-only) and (b) nocturnal hypoglycemia, and (c) hypoglycemic episode incidence by time of day; all episodes.

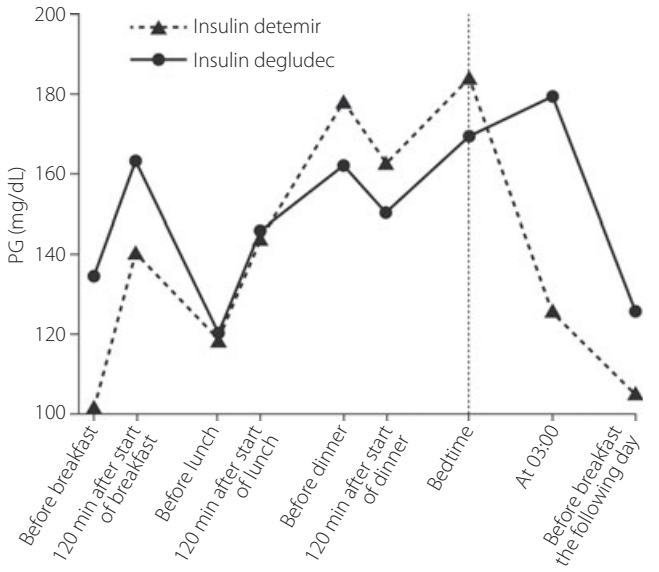

Figure 3 | Nine-point self-monitored plasma glucose profiles at 6 weeks. PG, plasma glucose.

consistent with data from non-Japanese type 1 diabetes populations[15,16]. Nocturnal hypoglycemia is an important issue in clinical practice – non-adherence to insulin therapy was associated with hypoglycemia risk, among other factors, in a survey of insulin-treated diabetes patients in a number of countries including Japan[20], whereas non-severe nocturnal hypoglycemia is associated with absenteeism and lost productivity, and frequently results in patients reducing their insulin dose[21].

In type 1 diabetes patients treated with rapid-acting insulin analogs in basal-bolus therapy, insulin levels during the night are largely isolated from bolus insulin doses and thus nocturnal hypoglycemia is a good reflection of the hypoglycemic risk resulting from the basal insulin component. The consistent observation of low rates of nocturnal hypoglycemia with insulin degludec is likely to be explained by examination of the pharmacokinetic profiles of different insulins. Insulin degludec has a terminal half-life in Caucasian patients of 25.4 h, compared with 12.5 h for insulin glargine, and a very flat and stable profile in steady-state once-daily dosing[12,13]. Exposure to insulin degludec is evenly distributed (~50:50) in the first and second 12-h intervals after dosing, whereas approximately 60% of exposure to insulin glargine, for example, occurs in the first 12 h after dosing[13]. The difference in nocturnal hypoglycemia in the present study might therefore reflect the fact that insulin detemir, administered in the evening, provides a greater supply of basal insulin during the night than in the daytime. This suggestion is supported by the data from SMBG profiles, which indicate that although night-time glucose levels increased in both groups from baseline (thus presumably reducing the risk of nocturnal hypoglycemia with both insulins), this change was numerically greater with insulin degludec than with insulin detemir. Analysis of incidence of hypoglycemic events by time of

day showed a marked difference between insulin groups at all night-time intervals, with a particular excess of events in the insulin detemir group in the late night/very early morning period.

As an exploratory study, the present trial was subject to certain limitations, most notably its short duration (6 weeks) and limited sample size. The short duration precluded the use of change in HbA_{1c} levels as an efficacy end-point. In addition, the present study was open-label in design – a necessity because the administration devices for the two insulins are readily distinguishable in appearance and so a double-blind study would have required a double-dummy technique, resulting in an unacceptable number of injections and increased complexity for participants. This means that investigators and participants were aware of treatment assignments, and might have been cautious when adjusting doses of insulin degludec, evidenced by the smaller number of patients reaching FPG target. Overall, investigators might have been conservative in titrating insulin doses, as this trial did not use a formal treat-to-target approach, and because of the length of the trial, might not have reached a dose sufficient to reach target. No data are available to determine whether incidence of hypoglycemia or other adverse events might have been under- or over-reported with insulin degludec in the present open-label trial.

We can conclude from the present study that insulin degludec would represent an effective and well-tolerated treatment option in Japanese patients with type 1 diabetes, does not appear to be associated with any safety concerns and can be initiated with a unit-for-unit dose transfer in patients currently receiving another basal insulin. Insulin degludec appears to be associated with a lower rate of nocturnal hypoglycemia than does insulin detemir. This finding requires confirmation in larger-scale trials in Japanese patients, but is nevertheless encouraging.

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