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ORIGINAL ARTICLE

Insulin degludec: four times lower pharmacodynamic variability than insulin glargine under steady-state conditions in type 1 diabetes

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Aims: Insulin degludec (IDeg) is a new-generation basal insulin with an ultra-long duration of action. We compared the pharmacodynamic (PD) variability of IDeg and insulin glargine (IGlar) under steady-state conditions.

Methods: Day-to-day variability in glucose-lowering effect was investigated in 54 subjects with type 1 diabetes who underwent a 24-h euglycaemic glucose clamp on the 6th, 9th and 12th day of treatment with 0.4 U/kg of IDeg or IGlar once daily. Within-subject variability was estimated using a linear mixed model on log-transformed PD endpoints derived from the glucose infusion rate (GIR) profiles during the clamps.

Results: For IDeg the day-to-day variability in glucose-lowering effect was four-times lower than for IGlar for total metabolic effect ($AUC_{GIR,0\text{-}24h,SS}$, CV 20% vs. 82%) and for the last 22 h [$AUC_{GIR,2\text{-}24h,SS}$ (not influenced by intravenous insulin during the clamp), CV 22% vs. 92%]. Furthermore, lower variability in the maximum effect was observed for IDeg vs. IGlar ($GIR_{max,SS}$, CV 18% vs. 60%). The lower within-subject variability of IDeg was consistent over time (CVs of 33% for $AUC_{GIR,0\text{-}2h,SS}$, 32% for $AUC_{GIR,10\text{-}12h,SS}$ and 33% for $AUC_{GIR,22\text{-}24h,SS}$), whereas the variability of IGlar was higher and increased substantially 8 h post-dosing (CVs of 60% for $AUC_{GIR,0\text{-}2h,SS}$, 135% for $AUC_{GIR,10\text{-}12h,SS}$ and 115% for $AUC_{GIR,22\text{-}24h,SS}$).

Conclusions: These results show that IDeg has a significantly more predictable glucose-lowering effect from day to day than IGlar.

Keywords: insulin degludec, insulin glargine, pharmacodynamics, pharmacokinetics, type 1 diabetes

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Introduction

Insulin secretion in healthy subjects is tightly regulated and maintains plasma glucose concentrations in the euglycaemic range (approximately 4–6 mmol/l). Formulations of exogenously administered insulin have been developed that can be combined in regimens (basal and bolus insulins) to approximate the plasma insulin kinetics produced by endogenous insulin secretion. However, although these insulin products have been improved during recent decades, clinical experience indicates that subcutaneous administration of insulin often does not result in a reproducible metabolic effect even when injected at the same dose under comparable conditions. Relatively few studies have assessed the variability of insulin absorption after subcutaneous administration [1–7], and even fewer have assessed the variability in the glucose-lowering effect of insulin in healthy subjects [8], in people with type 1 diabetes [9] and in people with type 2 diabetes [10]. Within-subject day-to-day variability corresponds to the difference in the glucose-lowering effect from one injection to another under comparable conditions in the same patient. Day-to-day differences in PD effect are largely attributable to differences in absorption rate, which in turn is partly attributable to the physico-chemical properties of the insulin, as well as physiological factors such as injection site, blood flow rate, skin temperature, exercise, hydration, etc. For insulin titration, it is important that the same insulin dose elicits as similar a glucose-lowering effect as possible following each administration. Consequently, an insulin with a more predictable glucose-lowering effect should provide greater confidence in safely adjusting doses, and thereby be more effective in achieving recommended glycaemic targets.

The aim of this study was to compare the within-subject day-to-day variability in the glucose-lowering effect at steady state of the ultra-long-acting insulin degludec (IDeg) with that of insulin glargine (IGlar). The ultra-long effect of IDeg is primarily attributable to the slow release of IDeg monomers from soluble multi-hexamers that form after subcutaneous injection, resulting in a flat and stable glucose-lowering effect with an ultra-long duration of action at steady state [11–13].

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Results of this study were presented in abstract/poster form at the 71st scientific sessions of the American Diabetes Association, San Diego, California, 24–28 June 2011, and at the 47th Annual Meeting of the European Association for the Study of Diabetes, 20–24 September 2010, Stockholm, Sweden.

Materials and Methods

Study Design

This was a randomized, single-centre, parallel group, double-blind trial comparing the within-subject day-to-day variability in the glucose-lowering effect between IDeg and IGlar at steady state in subjects with type 1 diabetes. The study was approved by the local ethics committee and health authorities and carried out in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice guidelines [14] and the Declaration of Helsinki [15]. Written informed consent was obtained from all the subjects before any study-related activities. The trial is registered at ClinicalTrials.gov (ID number; NCT00961324).

Subjects

Study participants were enrolled at Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany. Eligible subjects were men and women 18–65 years of age (both inclusive), diagnosed with type 1 diabetes for a minimum of 12 months before inclusion in the trial, treated with multiple daily insulin injections ≥12 months (total daily insulin <1.2 U/kg/day and daily basal insulin ≥0.2 U/kg/day), having a glycosylated haemoglobin (HbA1c) ≤10.0%, a body mass index (BMI) of 18.0–28.0 kg/m^2 and a fasting C-peptide <0.3 nmol/l. Individuals with clinically significant concomitant diseases, a history of recurrent major hypoglycaemia or hypoglycaemic unawareness, or those who were pregnant or breast-feeding, were excluded from participation.

Interventions

Before the first administration of study medication, subjects were not allowed to use insulin detemir or IGlar in the preceding 48 h, and neutral protamine Hagedorn (NPH) insulin or other intermediate-acting insulin products or any premixed insulin products in the preceding 22 h in order to ensure washout of these insulins. Subjects were randomly allocated to 0.4 U/kg body weight (BW) of either IDeg (100 U/ml; Novo Nordisk, Bagsvaerd, Denmark) or IGlar (Lantus, 100 IU/ml; Sanofi, Frankfurt, Germany) once daily for 12 days. IDeg and IGlar were administered by subcutaneous injection into a lifted skin fold in the thigh. All injections were done at approximately 20:00 hours and were performed with a syringe by a person otherwise not involved in the study to keep the double-blind character of the study. All basal insulin administrations were done by staff from the investigational site (either under in-patient or out-patient conditions), whereas subjects self-administered bolus injections of insulin aspart (IAsp) for prandial glucose control during the treatment period except on the days where glucose clamps were performed. On these days, no prandial insulin was used. Steady-state pharmacokinetic (PK) and pharmacodynamic (PD) responses were evaluated through the use of identical euglycaemic glucose clamps on treatment days 6, 9 and 12.

Clamp Procedure

For the euglycaemic glucose clamps, subjects attended the clinical site in a fasting state (no food intake in the 12 h before dosing) and were connected to a Biostator (MTB Medizintechnik, Amstetten, Germany). Approximately 5 h before dosing, subjects received a variable intravenous (i.v.) infusion of either human regular insulin (Actrapid, Novo Nordisk, Bagsvaerd, Denmark) or glucose to obtain a blood glucose clamp target of 5.5 mmol/l (100 mg/dl). The i.v. insulin infusion (if any) was stopped post-dose when blood glucose decreased by 0.3 mmol/l (5 mg/dl); glucose infusion was then initiated. The clamp continued for 24 h post-dosing and the glucose infusion rate (GIR) necessary to keep blood glucose levels constant was recorded every minute for these 24 h. The euglycaemic glucose clamp procedure was stopped earlier if blood glucose increased to >13.9 mmol/l (250 mg/dl) without any glucose having been administered for at least 30 min. Throughout the clamp procedure, subjects remained fasting (apart from water) and in a supine position. Blood samples for blood glucose measurements were taken every 30 min and for PK analysis (serum levels of IDeg or IGlar, depending on the study medication applied) every hour (including pre-dose).

Assessments

The primary endpoint was the within-subject variability in the area under the GIR curve during one dosing interval (0–24 h) at steady state ($AUC_{GIR,0\text{-}24h,SS}$). Secondary PD endpoints included $AUC_{GIR,2\text{-}24h,SS}$, the fluctuation around the mean GIR level at steady state ($AUCF_{GIR,0\text{-}24h,SS}$) and maximum GIR at steady state ($GIR_{max,SS}$). Furthermore, to investigate whether within-subject variability was consistent over 24 h, the within-subject variability of AUC_{GIR} in 2-h intervals ($AUC_{GIR,0\text{-}2h,SS}$, $AUC_{GIR,2\text{-}4h,SS}$, $AUC_{GIR,4\text{-}6h,SS}$, ... $AUC_{GIR,20\text{-}22h,SS}$, $AUC_{GIR,22\text{-}24h,SS}$) was analysed in a *post-hoc* analysis. Secondary PK endpoints included area under the serum concentration-time profiles during one dosing interval (0–24 h) at steady state ($AUC_{IDeg,0\text{-}24h,SS}$ and $AUC_{IGlar,0\text{-}24h,SS}$). Serum IDeg concentrations were measured using a specific enzyme-linked immunosorbent assay (ELISA) and serum IGlar concentrations were measured using a luminescent oxygen channelling immunoassay (LOCI). Safety endpoints included adverse events, hypoglycaemic episodes, injection-site reactions, electrocardiogram, vital signs, physical examinations and laboratory safety parameters. Hypoglycaemia was defined as rates of self-reported confirmed hypoglycaemia (plasma glucose <56 mg/dl [3.1 mmol/l] or severe hypoglycaemia requiring assistance) and nocturnal confirmed hypoglycaemia (time of onset between 00:01 and 05:59 hours).

Statistical Methods

All statistical analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, NC, USA). The primary endpoint, $AUC_{GIR,0\text{-}24,SS}$, was derived from the individual GIR profiles measured on treatment days 6, 9 and 12 during the three euglycaemic clamp visits. The primary endpoint was calculated as the area under the smoothed GIR curve using the linear trapezoidal technique on interpolated points. The primary analysis compared differences between IDeg and IGlar in within-subject variability (day-to-day variability) of

$AUC_{GIR,0\text{-}24h,SS}$. In order to account for heteroscedasticity, the primary endpoint was log-transformed and analysed in a linear mixed model using PROC MIXED with insulin type and period as fixed effects, subject as a random effect depending on insulin type and an error variance (within-subject variability) also depending on the insulin type. The test for no difference in the within-subject variability between the two insulin types was evaluated in an *F*-distribution, with a significance level of 5%.

Coefficients of variation (CV%) were derived from the within-subject variability σ^2 using the formula $CV\% = 100\% \times \sqrt{\left(\exp\left(\sigma^2\right) - 1\right)}$. The difference in within-subject variability between the two insulin types was assessed as the ratio between the CVs.

The secondary endpoints, $AUC_{GIR,2\text{-}24h,SS}$, $AUCF_{GIR,0\text{-}24h,SS}$ and $GIR_{max,SS}$ were analysed using the same model as for the primary endpoint. In the *post-hoc* analysis, we analysed the within-subject variability of AUC_{GIR} in separate 2-h intervals ($AUC_{GIR,0\text{-}2h,SS}$, $AUC_{GIR,2\text{-}4h,SS}$, $AUC_{GIR,4\text{-}6h,SS}$, ... $AUC_{GIR,20\text{-}22h,SS}$, $AUC_{GIR,22\text{-}24h,SS}$) using PROC MIXED. However, with the changes from the primary model, the error variance was assumed to follow a heavy-tailed *t*-distribution with four degrees of freedom and the test for no difference in within-subject variability between insulin types was evaluated using a likelihood-ratio test. The rationale for using a *t*-distribution is that the division of the AUC in 2-h intervals will *per se* generate outliers as calculation of the AUC in shorter intervals is more influenced by random fluctuations in the GIR curve, which potentially can influence the estimate of within-subject variability. The *t*-distribution with its heavier tail compared to the normal distribution is often used in robust regression, where inference is not overly influenced by outliers. Hence as sensitivity analyses, the endpoints $AUCF_{GIR,0\text{-}24h,SS}$ and $GIR_{max,SS}$ were analysed assuming the error variance followed a heavy-tailed *t*-distribution with four degrees of freedom. PK endpoints ($AUC_{IDeg,0\text{-}24h,SS}$ and $AUC_{IGlar,0\text{-}24h,SS}$) were analysed using the primary model (excluding insulin type).

An illustrative analysis of the potential risk caused by a hypothetical change in the glucose-lowering effect for each insulin type was made using the cumulative normal distribution $\phi_{0,\sigma^2}(z)$ on the log scale with a mean μ for the glucose-lowering effect, a variance σ^2 believed to be the estimated within-subject variability from the primary model and z denoting an arbitrary level of the glucose-lowering effect. Hereby, $\phi_{0,\sigma^2}(z)$ would calculate the risk of being lower than z in the normal distribution and $1 - \phi_{0,\sigma^2}(z)$ would calculate the risk of being higher than z. Using the property of the normal distribution by standardizing the mean to zero and the property of the logarithm function, the risk of a 50% reduction in the glucose-lowering effect on the original scale would be calculated as $\phi_{0,\sigma^2}\left(\log(0.5)\right)$ and a doubling of the glucose-lowering effect would be calculated as $1 - \phi_{0,\sigma^2}\left(\log(2)\right)$ dependent on the estimated within-subject variability σ^2. Assuming that the risk was uniform during a year, the number of hypothetical events throughout a year caused by the changes in the glucose-lowering effects (i.e. higher or lower than the hypothetical level z) was simply calculated as risk times 365 days.

Results

Demographic and Baseline Characteristics of the Subjects

There were no clinically relevant differences in baseline or demographic characteristics between subjects in the two treatment groups (table 1). A total of 68 subjects were screened, of whom 54 were randomized and 52 subjects completed the trial (25 on IDeg and 27 on IGlar). Two subjects in the IDeg group withdrew consent; one subject withdrew on day 5 before the first clamp and one subject withdrew after the first clamp. For the latter subject, the data for the first clamp were used in the analysis.

Pharmacodynamics

The within-subject variability for $AUC_{GIR,0\text{-}24h,SS}$ was four-times lower for IDeg (CV 20%) compared with IGlar (CV 82%), ($p < 0.0001$) (table 2). The differences in variability were even more pronounced when the first 2 h of the glucose clamp procedure were excluded from the assessment ($AUC_{GIR,2\text{-}24h,SS}$) (IDeg 22% vs. IGlar 92%; $p < 0.0001$) (table 2). The within-subject variability of the level of maximum effect ($GIR_{max,SS}$) was also significantly lower for IDeg (CV 18%) than for IGlar (60%), ($p < 0.0001$) (table 2).

Subject-specific CVs (%) for $AUC_{GIR,0\text{-}24h,SS}$ were consistently lower for IDeg compared with IGlar when the individual CVs (%) were compared in ranked order (figure 1). Furthermore, the data showed that the estimated difference in within-subject variation between IDeg and IGlar is driven by the majority of the subjects in the IGlar treatment group rather than entirely by the one extreme value seen for IGlar (figure 1).

Table 1. Pharmacodynamic variability of baseline and demographic characteristics of the two treatment groups.

	Insulin degludec (n = 27)	Insulin glargine (n = 27)
Sex (% men)	85	93
Race (% white)	96	100
Age (years)	40	36
BMI (kg/m^2)	24.6 (±2.4)	24.8 (±2.0)
Baseline HbA1c (%)	7.8 (±1.1)	7.5 (±0.8)
C-peptide (nmol/l)	0.02 (±0.03)	0.03 (±0.05)

Mean (±SD) if not indicated otherwise.

Table 2. Pharmacodynamics of the two treatment groups.

	Within-subject coefficient of variation (%)		
	Insulin degludec	Insulin glargine	p-value
$AUC_{GIR,0\text{-}24h,SS}$	20	82	<0.0001
$AUC_{GIR,2\text{-}24h,SS}$	22	92	<0.0001
$GIR_{max,SS}$	18	60	<0.0001
$AUCF_{GIR,0\text{-}24h,SS}$	31	73	<0.0001

$AUC_{GIR,0\text{-}24h,SS}$, area under the glucose infusion rate curve from 0–24 h at steady state; $AUC_{GIR,2\text{-}24h,SS}$, area under the glucose infusion rate curve from 2–24 h at steady state; $GIR_{max,SS}$, maximum glucose infusion rate at steady state; $AUCF_{GIR,0\text{-}24h,SS}$, fluctuation of the glucose infusion rate curve from 0–24 h at steady state.

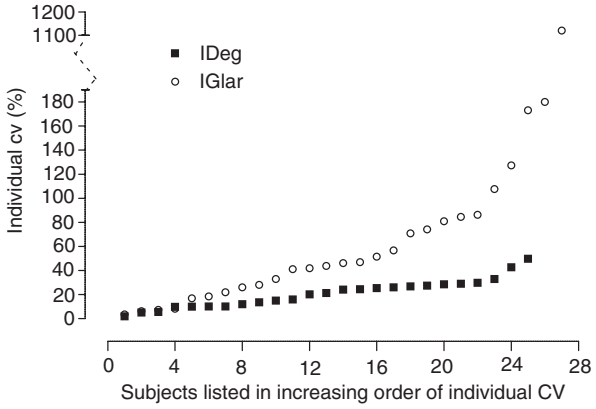

Figure 1. Subject specific day-to-day variability in $AUC_{GIR,0\text{-}24h,SS}$.

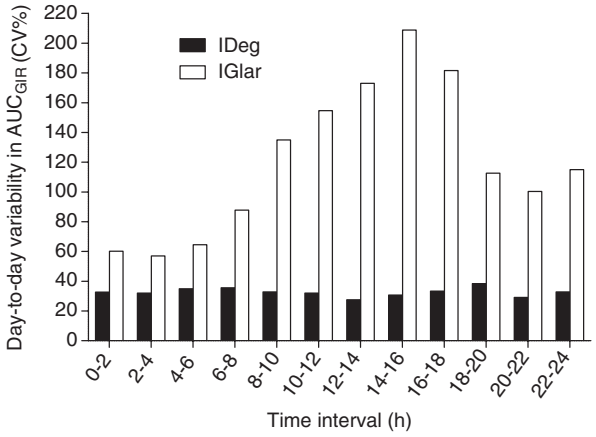

Figure 2. Day-to-day variability in glucose-lowering effect over 24 h at steady state.

The day-to-day variability of IDeg was consistently low over the entire 24-h period, whereas the variability of IGlar was significantly higher and increased substantially 6–8 h after dosing reaching a maximum at 14–16 h after dosing (figure 2). The lower within-subject variability of IDeg was consistent over time (CVs of 33% for $AUC_{GIR,0\text{-}2h,SS}$, 32% for $AUC_{GIR,10\text{-}12h,SS}$ and 33% for $AUC_{GIR,22\text{-}24h,SS}$), whereas the variability of IGlar was higher (CVs of 60% for $AUC_{GIR,0\text{-}2h,SS}$, 155% for $AUC_{GIR,10\text{-}12h,SS}$ and 115% for $AUC_{GIR,22\text{-}24h,SS}$). In addition, the day-to-day variability in the GIR fluctuations around the mean GIR level during the 24-h dosing interval at steady state ($AUCF_{GIR,0\text{-}24h,SS}$) was significantly lower for IDeg (CV 31%) than for IGlar (CV 73%), ($p < 0.0001$). The results of the sensitivity analyses assuming a robust *t*-distributed error variance confirmed the significantly lower day-to-day variability for IDeg as compared to IGlar for $AUC_{GIR,0\text{-}24,SS}$ (IDeg 23% vs. IGlar 72%; $p < 0.0001$) as well as for $GIR_{max,SS}$ (IDeg 21% vs. IGlar 53%; $p < 0.0001$).

Total metabolic effect ($AUC_{GIR,0\text{-}24h,SS}$) tended to be higher with IDeg than with IGlar as the overall estimated geometric mean for the primary endpoint ($AUC_{GIR,0\text{-}24,SS}$) was 2612 mg/kg [95% CI: 2162–3155 mg/kg] for IDeg and 1948 [95% CI: 1397–2717 mg/kg] for IGlar (i.e. a ratio between IDeg and IGlar for total metabolic effect of 1.34 [95% CI: 0.92–1.95]). The overall estimated geometric mean for $GIR_{max,SS}$ was 2.73 mg/(kg*min) [95% CI: 2.32–3.20 mg/(kg/min)] for IDeg and 2.37 [95% CI: 1.91–2.95 mg/(kg*min)] for IGlar.

Based on the estimated within-subject CV of the maximum glucose-lowering effect ($GIR_{max,SS}$, table 2), the projected risk of experiencing more than double the usual maximum effect on any given day (i.e. potential hypoglycaemia) is <0.1% for IDeg and 11% for IGlar. Based on the estimated within-subject CV of the total glucose-lowering effect ($AUC_{GIR,0\text{-}24h,SS}$, table 2), the projected risk of experiencing less than half the average effect on any given day (i.e. potential hyperglycaemia) is <0.1% for IDeg and 17% for IGlar.

Pharmacokinetics

In line with the PD findings, a trend for lower within-subject variability with IDeg versus IGlar was observed for the PK endpoints at steady state, $AUC_{IDeg,0\text{-}24h,SS}$ and $AUC_{IGlar,0\text{-}24h,SS}$ (data not shown).

Safety

IDeg and IGlar were well tolerated; no serious adverse events were reported in either group. Overall rates of adverse events were low, similar for IDeg and IGlar, with no specific patterns or clustering. No injection-site reactions or severe hypoglycaemic events were reported. In total, 100 confirmed hypoglycaemic episodes were observed with IDeg compared with 95 episodes with IGlar. Fewer confirmed nocturnal hypoglycaemic episodes were reported for IDeg (16 episodes in 9 subjects) than IGlar (26 episodes in 13 subjects). The observed number of hypoglycaemic episodes may be artificially high due to the fixed dosing level of 0.4 U/kg of IDeg and IGlar.

Discussion

The aim of this trial was to compare within-subject day-to-day variability in the glucose-lowering effect of IDeg with IGlar at steady state, and at clinically relevant doses, in subjects with type 1 diabetes.

The glucose-lowering action of IDeg at steady state showed four-times lower day-to-day variability during 0–24 h ($AUC_{GIR,0\text{-}24h,SS}$) and 2–24 h ($AUC_{GIR,2\text{-}24h,SS}$) as compared to IGlar. All other PD endpoints were supportive of the primary analysis; statistically significantly lower within-subject variability of $GIR_{max,SS}$ and fluctuation around the mean GIR at steady state ($AUCF_{GIR,0\text{-}24h,SS}$) were also found for IDeg versus IGlar. Furthermore, a *post-hoc* analysis showed that the day-to-day variability of IDeg was consistently low over the entire 24-h period, whereas the variability of IGlar was significantly higher and increased substantially 6–8 h after dosing, reaching a maximum 14–16 h after dosing. Within-subject variability of the PK endpoints (IDeg vs. IGlar) was also in agreement with the results from the primary analysis.

The difference in within-subject variability is expected to be of clinical relevance and to have an impact upon the risk of both hyper- and hypoglycaemia for the individual patient, as

suggested by our illustrative analyses of projected frequency rates for excessively high maximal and excessively low overall glucose-lowering effect. Although caution should be taken when extrapolating from experimental situations to clinical practice, it is worth noting that the predicted hypoglycaemia risks are qualitatively consistent with the results of clinical trials in which IDeg, at similar HbA1c levels, has been associated with significantly reduced rates of nocturnal [16–18] and overall [17] hypoglycaemia compared with IGlar in subjects with type 1 [16,18] and type 2 diabetes [17], treated with basal–bolus regimens . A lower variability of effect would be a major advantage when titrating the individual insulin dose and might provide a mechanistic explanation of the differences in hypoglycaemia incidence observed in the clinical trials.

The differences in within-subject variability are likely to be related to differences in mechanism of protraction; when IDeg is injected into the subcutaneous tissue, the formation of soluble multihexameric chains occurs at the injection site, with these complexes subsequently dissociating slowly to release monomers, which enter the circulation [11]. In contrast, IGlar forms microprecipitates after injection that must redissolve before absorption and these processes are inherently variable [19]. It is noteworthy that a previous trial also showed a higher variability of IGlar versus insulin detemir, which, similarly to IDeg, also stays in solution after injection in the subcutaneous tissue [20]. In that study, CV% values for IGlar were lower than those observed here (CV in $AUC_{GIR,0\text{-}24h}$ was 48% in the previous study vs. 82% in this study) [20]. While this might partly be due to erratic scattering of results between studies, another reason may lie in the different study design. This trial studied variability under steady-state conditions, whereas previous studies on insulin PD variability have been single-dose trials. For insulins with a duration of action >24 h, steady-state reflects the clinical situation and is the most appropriate way to evaluate PD properties, including variability. During steady state, the metabolic effect of an ultra-long-acting insulin at a given time-point will be contributed to by absorption from several previous injections, so any anomaly in the absorption rate of one injection can potentially be (partly) neutralized by absorption from other injections. In contrast, the PD effect of IGlar endures for 24 h or slightly more in some, but not all, injections [21,22]. Thus, at steady state the metabolic effect of IGlar will be determined by two injections for a short time post-dosing after most, but not all, injections. After a couple of hours post-dosing, any effect of the previous injection will have diminished, with the remaining effect being the result of a single injection. This might explain why the variability of IGlar substantially increases ~8 h post-dosing (figure 2). Variability in the duration of action of IGlar could also at least partly explain the higher variability of IGlar in this (steady state) study compared to previous (single-dose) studies.

Another potential explanation for disparities across studies in the variability of IGlar might be the presence of a few extreme CV-values. Indeed, one subject in this study showed very high variability with IGlar (figure 1). Similar extreme values in variability were reported for IGlar previously [8] and might occasionally occur with the formation of microprecipates [19]. To test whether the observed differences between IDeg and IGlar in our primary analysis were not solely dependent on certain extreme values, a *post-hoc* statistical model assuming a *t*-distribution for the error variance (an ANOVA model less sensitive to extreme values) was applied. This confirmed the highly statistically significant difference in variability between the two insulins ($p < 0.0001$ for $AUC_{GIR,0\text{-}24h,SS}$ and $GIR_{max,SS}$).

This trial has strengths and limitations. The strengths include investigation under steady-state conditions, and the use of patients with type 1 diabetes in whom there is a lack of endogenous insulin production to confound the results. Therefore, the observed differences in day-to-day variability largely reflect the absorption mechanisms of the exogenously administered insulins.

A limitation of this study is the difficulty in transferring the results from an experimental clamp setting to clinical reality. As noted, clinical studies show a lower rate in (nocturnal) hypoglycaemia with IDeg compared with IGlar [16–18], but it is not possible to attribute this clinical difference solely to the difference in variability between the two insulins. It could also partly be due to the different shape of the PD profiles, with IDeg showing less peak action and a more evenly distributed effect over 24 h than IGlar under steady-state conditions as described earlier [12,13] and also observed in this study.

One of the difficulties of clamp studies with basal insulins under steady-state conditions is to establish stable experimental conditions pre-dosing. Intravenous insulin had to be used to establish the target glucose clamp level in some experiments, whereas in others glucose had to be infused. In line with previous publications, we therefore computed the endpoint $AUC_{GIR,2\text{-}24h,SS}$, which represents the time period where the recorded action is not influenced by insulin infused during initiation of the clamp procedure. The within-subject variability for IDeg was similar for $AUC_{GIR,2\text{-}24h,SS}$ and $AUC_{GIR,0\text{-}24h,SS}$ suggesting that the estimated within-subject variability for IDeg is robust and probably represents the variability across the whole 24-h period as one dosing period. In contrast to this, the within-subject variability of IGlar became even higher when the first 2 h were excluded, in line with a previous study investigating the variability of insulin detemir versus NPH and IGlar [9].

One final limitation of this trial was that it had to be done as a parallel rather than a cross-over design. To investigate variability, three replicate clamp procedures were required for a given insulin in a given subject, resulting in accumulated blood loss for sampling of approximately 440 ml/subject. Therefore, it was not possible to do another three clamp experiments with the other insulin in the same individual.

In conclusion, this study demonstrated that at steady state IDeg has a more predictable glucose-lowering effect from day to day compared with IGlar. This, together with the flat and more consistent distribution of metabolic effect over the 24-h dosing interval for IDeg, should facilitate titration with IDeg to lower fasting plasma glucose targets than achievable with IGlar, and likely contributes to the lower risk of hypoglycaemia observed in clinical trials.

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Conflict of Interest

T. H. has received research grants as well as fees for speaking and consulting from Novo Nordisk A/S. H. H. and S. R. are employed by and hold stock in Novo Nordisk A/S. The remaining authors have no conflicts of interest to declare.

T. H., L. N., and H. H. designed, conducted/collected the data, analysed and wrote the manuscript. L. H. and A. F. conducted/collected the data, analysed and wrote the manuscript. S. R. performed the analysis and wrote the manuscript.

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