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ORIGINAL ARTICLE

Ultra-long-acting insulin degludec has a flat and stable glucose-lowering effect in type 2 diabetes

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Aims: Insulin degludec (IDeg) is a new-generation, ultra-long-acting basal insulin that forms soluble multihexamers upon subcutaneous injection, resulting in a depot from which IDeg is absorbed slowly and continuously into circulation. This double-blind, two-period, incomplete block cross-over trial investigated the pharmacodynamic and pharmacokinetic properties of IDeg at steady state (SS) in people with type 2 diabetes.

Methods: Forty-nine subjects treated with insulin without concomitant oral anti-diabetic drugs were given IDeg (0.4, 0.6 and/or 0.8 U/kg) once daily for two 6-day periods, separated by an interval of 13–21 days. Following dosing on Day 6, subjects underwent a 26-h euglycaemic glucose clamp (Biostator®; clamp blood glucose level: 90 mg/dl; 5.0 mmol/l). Pharmacokinetic samples were taken until 120 h after last dosing.

Results: For all dose levels, the mean glucose infusion rate (GIR) profiles were flat and stable. The glucose-lowering effect of IDeg was evenly distributed over the dosing interval τ, with area under the curve (AUC) for each of the four 6-h intervals being approximately 25% of the total AUC ($AUC_{GIR,\tau,SS}$). Total glucose-lowering effect increased linearly with increasing dose. The blood glucose levels of all subjects stayed very close to the clamp target until end of clamp. The terminal half-life of IDeg was approximately 25 h at steady state. IDeg was well tolerated and no safety concerns were identified. No injection site reactions were reported.

Conclusions: IDeg has a flat and consistent glucose-lowering effect in people with type 2 diabetes.

Keywords: insulin analogues, pharmacodynamics, randomized trial, type 2 diabetes

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Introduction

While existing long-acting insulin analogues have major advantages in their pharmacodynamic profiles over neutral protamine Hagedorn (NPH) insulin, they still show a subtle peak effect and, in some individuals, they need to be injected twice daily to cover basal insulin requirements [1]. Consequently, there is a need for a further improved long-acting insulin product that can provide continuous, flat and stable insulin replacement over an entire 24-h period with one daily injection.

Insulin degludec (IDeg) is an ultra-long-acting basal insulin modified such that the amino acid residue threonine in position B30 of human insulin has been omitted, and the ε-amino group of lysine in position B29 has been coupled to hexadecanedioic acid via a glutamic acid spacer. This structure allows IDeg to form soluble and stable multihexamers resulting in a depot in the subcutaneous tissue after injection. The gradual separation of IDeg monomers from the multihexamers results in a slow and continuous delivery of IDeg from the subcutaneous injection site into the circulation [2,3]. Thus, IDeg is designed to have an ultra-long and flat glucose-lowering profile due to the prolonged and stable insulin absorption.

The main aim of this trial was to confirm the ultra-long and consistent pharmacodynamic response of IDeg over a range of three clinically relevant doses in subjects with type 2 diabetes. Assessment was based on the glucose infusion rate (GIR) profile during one 24-h dosing interval (τ) at steady state (SS).

Materials and Methods

This randomised, single-centre, double-blind, two-period, incomplete block crossover, multiple-dose trial evaluated the pharmacodynamic and pharmacokinetic dose–response relationship of IDeg 100 and 200 U/ml at steady-state conditions in subjects with type 2 diabetes. The present paper presents results for IDeg 100 U/ml, while results for IDeg 200 U/ml will be published elsewhere. Henceforth, IDeg refers to IDeg 100 U/ml. The trial protocol (trial NN1250-1987: registered at clinicaltrials.gov with number NCT01154881) was approved by the local health authority (Bundesinstitut für Arzneimittel und Medizinprodukte) and ethics committee (Ärztekammer Nordrhein) and was performed in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines.

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Participants

Study participants were enrolled at Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany. Eligible participants were men and women 18–70 years of age (both inclusive), diagnosed with type 2 diabetes for a minimum of 12 months prior to inclusion in the trial, treated with insulin alone (any type) and with no use of oral antidiabetic drugs (OADs) or glucagon-like peptide-1 (GLP-1) receptor agonists within 3 months prior to screening. At screening, participants were to have a glycated haemoglobin (HbA1c) $\leq$ 10.0%, a body mass index (BMI) $\leq$ 35.0 kg/m^2, serum creatinine levels <126 µmol/l (male) or <111 µmol/l (female), and a fasting C-peptide <1.0 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

After giving signed informed consent, eligible subjects were randomly allocated to two of the following four treatments in an incomplete block design: IDeg 100 U/ml 0.4 U/kg, IDeg 100 U/ml 0.6 U/kg, IDeg 100 U/ml 0.8 U/kg, and IDeg 200 U/ml 0.6 U/kg. IDeg was administered once daily for two 6-day periods separated by an interval of 13–21 days. The investigator and the subjects were blinded to trial treatment and a person not otherwise involved in trial conduct prepared the doses. IDeg was injected subcutaneously into a lifted skin fold on the anterior surface of the thigh, once daily at 20:00 hours by a qualified person, under either in-patient (first three doses and last dose) or outpatient conditions. In contrast, insulin aspart, used as bolus insulin during the treatment periods if needed, was self-administered by the subjects. Bolus insulin was not administered during the clamp procedure.

Before receiving the first IDeg dose, subjects underwent a wash-out period where usual basal insulin was not taken for at least 48 h (insulin detemir or insulin glargine) or for at least 22 h (NPH or premixed insulin). Body weight at the time of the first IDeg injection was used for calculation of all subsequent doses. After the last IDeg dose at the end of each treatment period (Day 6), subjects underwent a 26-h euglycaemic clamp, performed by means of a Biostator® (MTB Medizintechnik, Amstetten, Germany). The design of the clamp is illustrated in figure 1. In brief, the subjects, who remained fasting and stayed in a supine position during the entire glucose clamp, were connected to the Biostator 5–6 h before the sixth IDeg dose administration. Subjects' blood glucose concentrations were stabilised at the target level of 90 mg/dl (5.0 mmol/l) by a variable intravenous infusion of human regular insulin (Actrapid®) or glucose. Blood glucose had to be at the target level no later than 2 h before dosing. From 1 h before IDeg administration, the insulin infusion rate (if any) was reduced as much as possible while keeping the blood glucose concentration at the clamp target level. During the last 10 min before trial product administration, the infusion of insulin was tapered off and terminated immediately before IDeg administration (time zero). Blood glucose and the glucose infusion rate necessary to keep the blood glucose concentration at the target level of 90 mg/dl (5.0 mmol/l) were recorded every minute throughout the glucose clamp. The glucose clamp would have been terminated early if glucose concentration consistently exceeded 250 mg/dl (13.9 mmol/l) with no glucose infusion for the last 30 min (glucose escape). This did not occur for any subject at any dose level in this trial. Blood samples for determination of serum IDeg concentration were obtained pre-dose, 30 min post-dose and then at regular intervals during the glucose clamp (up to 26 h). After the end of the clamp, samples were taken at 30, 36, 48, 72, 96 and 120 h post-dose.

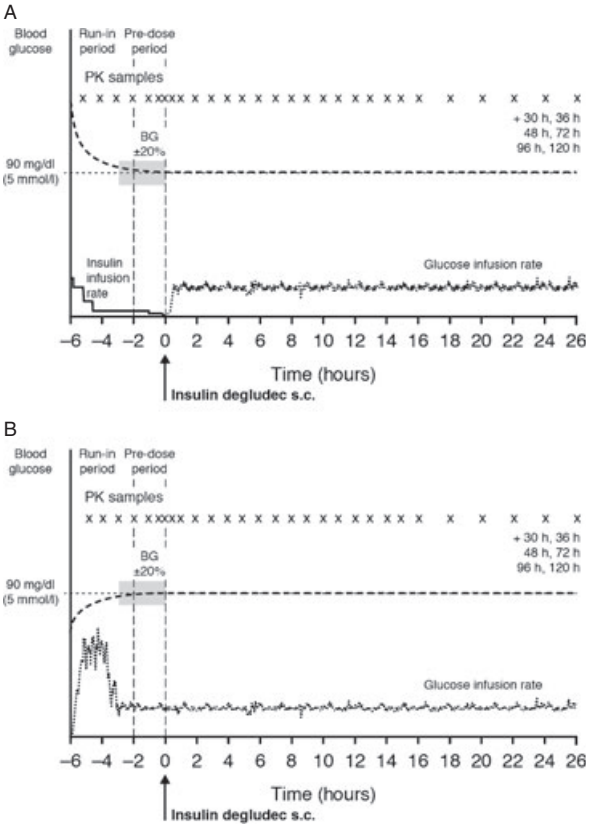

Figure 1. Design of the glucose clamp experiments. After the subjects had been connected to the Biostator®, their blood glucose (BG) levels were adjusted to the clamp target level of 90 mg/dl (5 mmol/l). If patients arrived with BG concentrations substantially above this target, an intravenous infusion of human regular insulin was given at a variable rate (Panel A). If the initial BG levels were lower than the target, glucose was infused at a variable rate by the Biostator (Panel B). The protocol prohibited the simultaneous use of intravenous insulin and glucose, so patients who received insulin intravenously did not receive glucose pre-dosing and vice versa. At least 1 h before the pre-dose period, BG concentrations had to be within a range of ±20% of the target. During the pre-dose period, which started from 2 h before dosing of study medication, the intravenous infusion of insulin (if any) was lowered as much as possible to keep BG concentrations at the target without having to infuse glucose (Panel A). Ten minutes before dosing the insulin infusion was tapered off and stopped completely no later than at dosing time. After dosing of the study medication, glucose infusion rates were registered every minute until the end of the clamp at 26 h post-dosing. Blood samples for the assessment of insulin degludec pharmacokinetics were drawn in regular intervals during the clamp experiment and up to 120 h post-dosing. PK, pharmacokinetic; s.c. subcutaneously.

The two treatment periods were separated by a washout period of 13–21 days counting from the last dosing in the first treatment period (Day 6). During this period, subjects resumed their usual insulin treatment.

Assessments

The primary endpoint was the area under the curve (AUC) for the GIR profile during one dosing interval (0–24 h) at steady state ($AUC_{GIR,\tau,SS}$). Secondary pharmacodynamic endpoints included duration of action and distribution of the glucose-lowering effect over the 24-h dosing interval at steady state. Secondary pharmacokinetic endpoints included area under the serum IDeg concentration–time profile during one dosing interval (0–24 h) at steady state ($AUC_{IDeg,\tau,SS}$), distribution of IDeg exposure over the 24-h dosing interval at steady state, pharmacokinetic 120-h profiles obtained following the last dose of each treatment period and terminal half-life for IDeg at steady state ($t_{1/2,IDeg,SS}$). Safety endpoints included adverse events, hypoglycaemic episodes, injection site reactions, electrocardiogram, vital signs, physical examination and laboratory safety parameters.

Serum IDeg concentrations were quantified by a specific sandwich enzyme-linked immunosorbent assay (ELISA). The capture antibody was a mouse monoclonal antibody specific for human insulin (HUI 001) and the detection antibody was a biotin-labelled monoclonal mouse antibody (NN454-1 F31) specific for IDeg.

Statistical Methods

$AUC_{GIR,\tau,SS}$ was calculated as the area under the smoothed GIR profile using the linear trapezoidal technique on interpolated points. GIR data were smoothed using the Loess smoothing technique using a fixed smoothing parameter of 0.25 and sampling with 5-min intervals. Last observation carried forward was used if there were missing values at the end of the assessment. The secondary pharmacodynamic endpoints were derived from the individual GIR profiles and blood glucose profiles at steady state. Distribution of the glucose-lowering effect over a 24-h dosing interval was quantified by estimating the ratio between the AUC for sub-areas under the GIR profiles (50:50 split and 25:25:25:25 split) versus the total AUC for the entire 24-h dosing interval ($AUC_{GIR,\tau,SS}$) as illustrated in figure 2. Duration of action was calculated as the time from IDeg administration until blood glucose concentration was consistently above 150 mg/dl (8.3 mmol/l) during the glucose clamp at steady state [4]. The pharmacodynamic dose–response relationship of $AUC_{GIR,\tau,SS}$ for IDeg was analysed using a linear mixed model with period, dose and dose squared as fixed effects, subject as a random effect, and an error variance depending on dose level.

The secondary pharmacokinetic endpoints were derived from the IDeg concentration–time profiles at steady state. $AUC_{IDeg,\tau,SS}$ was calculated as the area under the IDeg concentration–time profile using the linear trapezoidal technique based on observed values and actual measurement times between 0 and 24 h. Missing values were imputed using linear interpolation. Distribution of exposure over a 24-h dosing interval was quantified by estimating the ratio between the AUC for each of the two 12-h intervals versus AUC for the entire 24-h dosing interval ($AUC_{IDeg,\tau,SS}$). Clinically relevant time to steady state was estimated as time from first dose until serum IDeg trough concentrations exceeded 90% of the final plateau level [5].

Terminal half-life for IDeg at steady state ($t_{1/2,IDeg,SS}$) was estimated from the individual log–concentration–time profiles following the last dose of IDeg and calculated as $\log(2)/\lambda_{z,IDeg,SS}$.

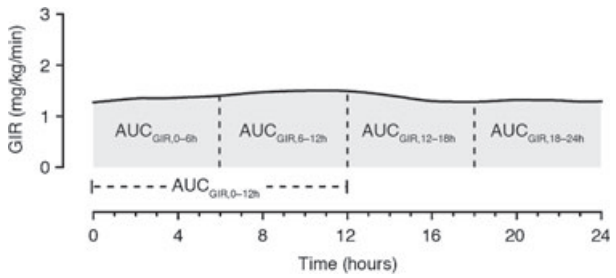

Figure 2. Illustration of sub-areas under GIR profiles (using either a 50:50 split or a 25:25:25:25 split). GIR, glucose infusion rate.

Results

Subjects

Of the 67 subjects screened, 49 were randomized to one of five predefined treatment sequences. All 49 subjects were exposed to IDeg; one subject withdrew for personal reasons after the first treatment period with 0.6 U/kg IDeg 100 U/ml. At baseline, subjects (82% males, 100% White) had a mean (SD) age of 58.7 (7.4) years, BMI 29.6 (3.0) kg/m^2, an HbA1c of 7.6% (0.9%), duration of diabetes 14.1 (7.4) years, serum creatinine concentration 83.3 (16.1) µmol/l and fasting C-peptide 0.44 (0.25) nmol/l. All subjects were treated with insulin prior to study participation, mainly basal–bolus treatment, and did not use OADs.

Pharmacodynamics

The 24-h mean GIR profiles for the three IDeg doses at steady state are shown in figure 3A. Flat and stable GIR profiles were obtained during the entire dosing interval for all three doses, and GIR increased with increasing dose (Table 1). $AUC_{GIR,\tau,SS}$ increased linearly with increasing dose in the dose range 0.4–0.8 U/kg IDeg (figure 4). The maximum GIR at steady state, $GIR_{max,SS}$, was 1.1, 1.7 and 2.4 mg/(kg·min) for IDeg 0.4 U/kg, 0.6 U/kg and 0.8 U/kg, respectively.

To evaluate the consistency of the glucose-lowering effect of IDeg over the entire 24-h dosing interval, AUC_{GIR} in shorter intervals of the 24-h dosing interval were compared with $AUC_{GIR,\tau,SS}$ (as illustrated in figure 2). The glucose-lowering effect of IDeg for the first 12 h after dosing was similar to that for the following 12 h, as $AUC_{GIR,0-12h,SS}/AUC_{GIR,\tau,SS}$ was close to 50% for all three dose levels. The evenly distributed glucose-lowering effect was further confirmed by the AUC_{GIR}

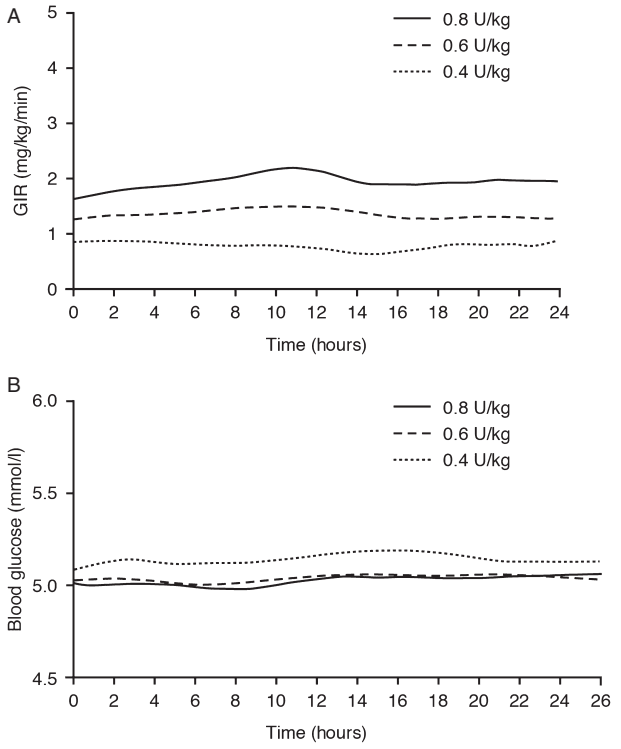

Figure 3. Pharmacodynamic profiles. A: 24-h GIR mean profiles – IDeg at steady state. B: 26-h blood glucose mean profiles – IDeg at steady state. GIR, glucose infusion rate; IDeg, insulin degludec.

for each of the four 6-h intervals contributing approximately 25% of the $AUC_{GIR,\tau,SS}$ at all three dose levels (Table 2).

Mean blood glucose profiles were almost horizontal throughout the 26-h clamp at a blood glucose level very close to the clamp target of 5.0 mmol/l (figure 3B). Moreover, individual blood glucose profiles were very close to the clamp target until end of clamp at all three dose levels (data not shown). The end of action (defined as blood glucose above 150 mg/dl or 8.3 mmol/l) did not occur for any of the subjects within the 26-h clamp period and therefore duration of action was beyond 26 h for all subjects.

Pharmacokinetics

As expected for a drug with a long half-life, IDeg trough levels (pharmacokinetic concentrations measured immediately before each dose) increased over the first days of treatment before reaching a plateau. Steady state was reached after 2–3 days of treatment in all subjects. At steady state, overall exposure of IDeg was unchanged from day to day (data not shown).

IDeg exposure, defined as the area under the serum IDeg concentration–time profile during one dosing interval ($AUC_{IDeg,\tau,SS}$) (Table 1) and the maximum observed serum IDeg concentration ($C_{max,IDeg,SS}$) increased with increasing dose at steady state. Both $AUC_{IDeg,\tau,SS}$ and $C_{max,IDeg,SS}$ increased proportionally with increasing dose (log–dose slopes of 0.93 $[0.82; 1.03]_{95\%\ CI}$ and 0.94 $[0.81; 1.08]_{95\%\ CI}$, respectively). Exposure to IDeg was evenly distributed over the 24-h dosing interval as $AUC_{IDeg,0-12h,SS}/AUC_{IDeg,\tau,SS}$ was close to 50% at all three dose levels (Table 1). Pharmacokinetic 120-h profiles obtained following the last dose showed that the serum IDeg concentration decreased slowly over time and was detectable for at least 120 h (5 days, end of observation period) for all subjects at all three dose levels (data not shown).

For the three IDeg dose levels, mean $t_{1/2,IDeg,SS}$ ranged from 24.4 to 26.8 h (Table 1). The terminal half-life across the three dose levels was estimated as 25.1 h.

Table 1. Pharmacodynamic and pharmacokinetic parameters.

	IDeg 0.4 U/kg	IDeg 0.6 U/kg	IDeg 0.8 U/kg
Number of subjects	22	37	21
Pharmacodynamics			
$AUC_{GIR,\tau,SS}$, mg/kg Geometric mean (CV)	827.5 (67.9)	1694.0 (55.9)	2482.3 (45.5)
Pharmacokinetics			
$AUC_{IDeg,\tau,SS}$, pmol·h/l Geometric mean (CV)	89643.2 (35.0)	130164 (22.6)	177408 (26.5)
$AUC_{IDeg,0-12h,SS}/AUC_{IDeg,\tau,SS}$ (%) Geometric mean (CV)	53.3 (4.1)	52.5 (5.0)	52.7 (5.3)
$t_{1/2,IDeg,SS}$, h Harmonic mean	24.6	24.4	26.8
Mean $t_{1/2}$, h Harmonic mean		25.1	

AUC, area under the curve; CV, coefficient of variation (%); GIR, glucose infusion rate; IDeg, insulin degludec; SS, steady state; $t_{1/2}$, half-life; τ, dosing interval.

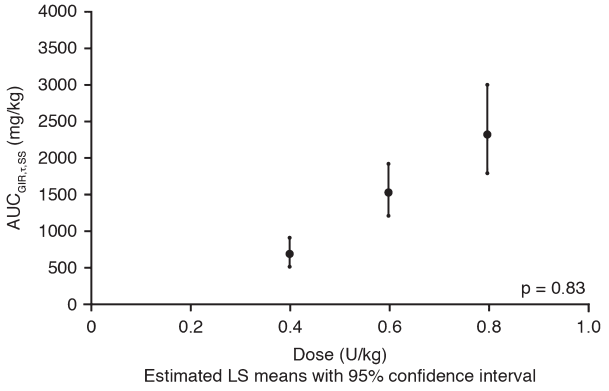

Figure 4. Estimated mean $AUC_{GIR,\tau,SS}$ vs. IDeg dose. Pharmacodynamic dose linearity at steady state: The endpoint is analysed using a linear mixed model with period, dose and dose squared as fixed effects, subject as random effect and an error variance depending on dose level. AUC, area under the curve; GIR, glucose infusion rate; IDeg, insulin degludec; SS, steady state; τ, dosing interval.

Safety

IDeg was well tolerated, and no safety concerns were identified. A total of 21 adverse events were reported and six of these were regarded as being possibly related to trial product (headache,

Table 2. Distribution of glucose-lowering effect over 24 h at steady state.

	Mean		
	IDeg 0.4 U/kg	IDeg 0.6 U/kg	IDeg 0.8 U/kg
Number of subjects	22	37	21
50:50 split			
$AUC_{GIR,0-12h,SS}$/ $AUC_{GIR,\tau,SS}$ % (CV)	48.9 (24.3)	53.0 (15.5)	50.4 (11.8)
25:25:25:25 split			
$AUC_{GIR,0-6h,SS}$/ $AUC_{GIR,\tau,SS}$ % (CV)	27.4 (25.4)	26.8 (24.8)	24.2 (17.2)
$AUC_{GIR,6-12h,SS}$/ $AUC_{GIR,\tau,SS}$ % (CV)	21.5 (39.4)	26.3 (15.7)	26.2 (17.7)
$AUC_{GIR,12-18h,SS}$/ $AUC_{GIR,\tau,SS}$ % (CV)	19.8 (45.0)	22.7 (27.9)	23.9 (18.1)
$AUC_{GIR,18-24h,SS}$/ $AUC_{GIR,\tau,SS}$ % (CV)	31.3 (41.0)	24.3 (21.0)	25.8 (25.3)

AUC, area under the curve; CV, coefficient of variation (%); GIR, glucose infusion rate; IDeg, insulin degludec; SS, steady state; τ, dosing interval.

nausea and vomiting). Hypoglycaemic episodes were defined as 'confirmed' when they were either classified as 'severe' as defined by the American Diabetes Association [6] or verified by a plasma glucose concentration <3.1 mmol/l (56 mg/dl). A total of six confirmed hypoglycaemic episodes were recorded in six subjects, none of which were severe. No injection site reactions were reported following treatment with IDeg. There were no clinically relevant safety findings in other safety parameters, including laboratory variables of haematology and biochemistry.

Discussion

This clinical trial characterised the pharmacodynamic and pharmacokinetic properties of insulin degludec in a range of clinically relevant doses in individuals with type 2 diabetes. The total glucose-lowering effect of IDeg increased linearly with increasing dose and extended beyond 26 h. The glucose-lowering effect of IDeg was flat and stable at all the dose levels investigated. Furthermore, the total exposure of IDeg increased proportionally with increasing dose, with a consistent distribution of the pharmacokinetic exposure at all the dose levels.

Because of the ultra-long duration of action of IDeg, relevant pharmacodynamic investigations can only be conducted at steady state, as the pharmacodynamic profile after single dose administration is not identical to that after repeated dose administrations. For this reason, the pharmacodynamic investigations were conducted on the sixth treatment day. It is technically challenging to establish stable conditions before insulin dosing under glucose clamp conditions. This is because one must compensate for the ongoing effect of previous insulin injections. Moreover, if the fasting blood glucose level is above the clamp target, the target blood glucose level has to be established using intravenous infusion of human regular insulin. In previous studies this intravenous insulin infusion was continued (at least for some time) post-dosing [7–9] which led to a significant impact on glucose infusion rate profiles in the first 2 h post-dosing [7,8]. We therefore modified the glucose clamp procedure so that the target blood glucose level had to be established at least 2 h before dosing, using intravenous infusion of either insulin or glucose (rather than both). Moreover, the insulin infusion (if any) was reduced as much as possible during the last hour before trial drug administration and stopped entirely at dosing time. With this procedure, an artificial increase in GIR early post-dosing, as seen in other studies [7], could be prevented.

Without this artificial increase, the steady-state pharmacodynamic profile of IDeg was virtually peakless in all three doses studied, as seen in figure 3A. In order to describe the flatness of the pharmacodynamic and pharmacokinetic profile, we compared exposure and the glucose-lowering effect of IDeg in the first 12 h post-dosing with the following 12 h of the 24-h dosing interval and observed a nearly perfect split around 50%. Furthermore, the glucose-lowering effect was similar in all the 6-h intervals within the 24-h dosing interval. Such a flat profile cannot be achieved by insulin preparations with duration of action around 24 h or shorter as physiologically, insulin absorption will always start from zero and, once peaked, return to baseline. The fluctuations in insulin levels (and thereby in glucodynamic effect) can be reduced when the effects of subsequent injections overlap. In fact, the half-life of approximately 25 h demonstrated in this study confirms the slow and consistent absorption of IDeg, leading to ultra-long duration of action. In accordance with a previously published trial [4] we defined end of action as the time from trial product administration until blood glucose concentration was consistently above 8.3 mmol/l (150 mg/dl) during the glucose clamp at steady state. End of action did not occur for any subject at any dose level as blood glucose did not exceed 8.3 mmol/l within the 26-h clamp period. Actually, the blood glucose levels of all subjects stayed very close to the clamp target until end of clamp. This confirms that the glucose-lowering effect of IDeg extends beyond 26 h.

A recent clinical trial characterised the pharmacodynamic response of IDeg during a 42-h euglycaemic clamp in individuals with type 1 diabetes [10]. In that trial, the glucose-lowering effect of IDeg extended beyond 42 h at all the dose levels investigated (0.4, 0.6 and 0.8 U/kg), with a total exposure similar to the total exposure in the present trial in type 2 diabetes. Relatively high serum IDeg concentrations were demonstrated 42 h after administration, both in the trial in type 1 diabetes and in the present trial in type 2 diabetes, and IDeg was detectable in serum for at least 120 h after the last injection. Since a clear relationship between exposure and glucose-lowering effect has been demonstrated for IDeg, duration of action in subjects with type 2 diabetes is expected to be beyond 42 h, similar to that observed for subjects with type 1 diabetes [10]. The ultra-long duration of action of IDeg was also confirmed in a 26-week clinical trial in people with type 2 diabetes. In this trial, intervals of 8–40 h were applied between IDeg injections without compromising glucose control (similar HbA1c and significantly lower fasting plasma glucose levels) or safety (similar rates of confirmed hypoglycaemia) in comparison to insulin glargine injected once daily at the same time each day [11]. Similarly, a study in people with type 2 diabetes investigating the efficacy and safety of IDeg

used just three times a week (e.g. injections on Mondays, Wednesdays and Fridays) showed similar improvements in glycaemic control and similar numbers of patients suffering from hypoglycaemia compared with insulin glargine used once daily [12]. These two studies indicate that efficacy and safety of IDeg will not be compromised even if patients omit an injection for 24 h.

One of the limitations of this study is the lack of a comparator. The main objective of this study with IDeg was to investigate the dose–response relationship which has already been studied for other basal insulins in people with type 2 diabetes [13,14]. When comparing the data across studies, it seems that IDeg indeed has a considerably longer duration of action than insulin glargine which, at a dose of 0.5 U/kg, showed small increases in blood glucose levels at the end of a 24-h clamp [14] and has a half-life of around 13 h [15]. In fact, another glucose-clamp study [10] compared the pharmacokinetic and pharmacodynamic properties of IDeg and insulin glargine in people with type 1 diabetes and confirmed the considerably longer half-life of IDeg (25.1 vs. 12.5 h).

Another limitation of all glucose clamp studies is the experimental set-up, which can make it difficult to relate study findings to clinical reality. Indeed, this study is a good example as we randomised patients to fixed-dose levels of IDeg for two periods of six consecutive days, which clearly is an experimental setting not reflecting the therapeutic use of IDeg. In a clinical setting, the dose of IDeg must be titrated and adjusted to meet the individual insulin needs without compromising safety, particularly in terms of hypoglycaemic episodes. Thus, the hypoglycaemic episodes that occurred in this trial could be considered 'artificial' due to the lack of individual basal insulin dose adjustments.

The equal distribution of IDeg glucose-lowering effect over 24 h with no apparent peaks and the four-times lower day-to-day variability in glucose-lowering effect compared with insulin glargine [10] should lead to reduced risk of overall and, particularly, nocturnal hypoglycaemia. Indeed, lower rates of nocturnal hypoglycaemia were observed in two recently presented long-term clinical studies with IDeg in subjects with type 1 diabetes [16] and type 2 diabetes [17].

Today, a proportion of people with diabetes may need two injections of basal insulin per day as has been discussed for currently available insulin analogues [18,19]. Even more frequent injections have been suggested for NPH insulin when combined with rapid-acting insulin analogues [20,21]. Currently available pharmacological data show that the duration of action of IDeg in clinically relevant doses exceeds well beyond 24 h in each and every individual studied, substantiating that IDeg is designed to be a once-daily basal insulin product suitable for all individuals with diabetes mellitus. This should offer patients the flexibility of varying the insulin injection time from day to day [11] and will contribute to the virtually peakless action in a 24-h treatment period, as demonstrated in this study.

In conclusion, ultra-long-acting IDeg has a flat and consistent glucose-lowering effect that is evenly distributed across a 24-h dosing interval. Moreover, IDeg has a duration of action in patients with type 2 diabetes, which allows for once-daily dosing as well as flexibility in the timing of administration.

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Conflict of Interest

T. H., S. G. B., H. H. and H. H. interpreted the data. T. H., H. H. and H. H. drafted the article. T. H., L. N., S. G. B., H. H. and H. H. revised the article. L. N. acquired the data. S. G. B., H. H. and H. H. analysed the data. H. H. and H. H. conceptualized and designed the study.

T. H. is a shareholder of Profil Institut für Stoffwechselforschung GmbH. Within the last year, the institute received research grants from the following pharmaceutical companies: Becton Dickinson, Biodel, Boehringer Ingelheim, Glaxo SmithKline, Hoffmann LaRoche, Eli Lilly, Lundbeck, Johnson & Johnson, Merck Sharpe & Dohme, Novo Nordisk, Roche Diagnostics, Sanofi Aventis and Servier. T. H. received travel grants, consulting fees and speaker honoraria from Novo Nordisk and Boehringer Ingelheim. L. N. is an employee at Profil Institut. S. G. B., H. H. and H. H. are employees and stockholders at Novo Nordisk A/S.

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