EXPERT OPINION

Comparison of the pharmacokinetic and pharmacodynamic profiles of insulin degludec and insulin glargine

Tim Heise[†], Ulrike Hövelmann, Leszek Nosek, Lidia Hermanski, Susanne G Bøttcher & Hanne Haahr
[†]*Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany*

Objectives: A medical need remains for a once-daily insulin with 24-h basal coverage in all patients. We characterize the steady-state (SS) pharmacokinetic/pharmacodynamic properties of insulin degludec (IDeg) versus insulin glargine (IGlar).

Research design and methods: In this controlled, single-center study, 66 type 1 diabetes patients were randomized to two 8-day periods of once-daily IDeg or IGlar at 0.4, 0.6 or 0.8 U/kg. At SS, subjects underwent a 42-h euglycemic glucose clamp (5.5 mmol/l; 100 mg/dl). Glucose infusion rate (GIR), distribution of GIR and half-life were assessed.

Results: Mean 24-h GIR profiles were flatter and more stable for all doses of IDeg versus IGlar. The evenly distributed glucose-lowering effect of IDeg was confirmed by the AUC_{GIR} across one dosing interval, as each of the four 6-h intervals across one dosing interval contributed ~ 25% of the $AUC_{GIR,\tau,SS}$. IGlar was most effective during the first 12 – 18 h after dosing. At SS, the half-life was 25.4 (IDeg) versus 12.1 h (IGlar). No safety concerns were identified for IDeg or IGlar.

Conclusion: IDeg has a longer half-life (> 25 h) than IGlar. Exposure and glucose-lowering effects are more stable and evenly distributed across one dosing interval for IDeg versus IGlar (Clinical trials.gov identifier: NCT01114542).

Keywords: euglycemic glucose clamp, insulin degludec, insulin glargine, pharmacodynamics, pharmacokinetics, type 1 diabetes

Expert Opin. Drug Metab. Toxicol. [Early Online]

1. Introduction

Currently available basal insulin analogs should be dosed once daily according to their label. However, results from clinical trials and findings in clinical practice show that their effect does not fully cover 24 h in all individuals, so some patients may benefit from, or even require, more frequent insulin dosing [1,2]. In addition, basal insulin analogs, such as insulin glargine (IGlar) and insulin detemir (IDet), while showing less peak effect than neutral protamine Hagedorn insulin, are still not peakless. Rather they are characterized by 24-h glucose-lowering effect profiles with periods of low action rising to a peak/plateau followed by a decline [3-5]. Furthermore, the within-patient variability of the glucose-lowering effect of IGlar was shown to be greater than IDet [6,7]. Therefore, an unmet medical need remains for basal insulin analogs with further optimized pharmacodynamic properties.

Insulin degludec (IDeg) is a basal insulin with a distinct absorption mechanism, where the formation of multi-hexamers after injection results in a soluble depot in

informa healthcare

the subcutaneous (s.c.) tissue from which IDeg monomers gradually separate [8,9]. IDeg was developed to achieve a very long duration of action with once-daily administration for all individuals. Previous studies under steady-state (SS) conditions have shown that IDeg has a four-times lower variability in glucose-lowering effect as compared with IGlar in subjects with type 1 diabetes mellitus (T1DM) [10] and provides a flat and stable glucose-lowering effect profile in subjects with type 2 diabetes mellitus (T2DM) [11]. This study aims to build on the results from these two previous Phase I trials by evaluating the dose-to-dose comparison in glucose-lowering effect between IDeg and IGlar across a broad range of doses. The primary aim of this study was to characterize the SS pharmacokinetic and pharmacodynamic properties of IDeg as compared to IGlar across one dosing interval within a therapeutically relevant dose range (0.4, 0.6 and 0.8 U/kg) in subjects with T1DM.

2. Patients and methods

2.1 Study design

This study was a randomized, single-center, double-blind, two-period, crossover, multiple dose trial conducted in subjects with T1DM (Clinical trials.gov identifier: NCT01114542). Prior to trial initiation, the protocol was reviewed and approved by the independent federal authority (Bundesinstitut für Arzneimittel und Medizinprodukte), according to local regulations, and by an independent ethics committee (Ärztekammer Nordrhein). The trial was performed in accordance with the Declaration of Helsinki and its amendments in force at the initiation of the trial. Informed consent was obtained in writing from all study participants before any trial-related activities.

2.2 Subjects

Eligible study participants were males and females aged between 18 and 65 years (both inclusive) with T1DM for a minimum of 12 months at inclusion, who had been treated with multiple daily insulin injections for ≥ 12 months (total daily insulin < 1.2 (I)U/kg/day and daily basal insulin ≥ 0.2 (I)U/kg/day). Eligible participants had a body mass index (BMI) of 18.0 – 28.0 kg/m^2 inclusive, a glycated hemoglobin (HbA_{1c}) level of ≤ 10.0% and a fasting C-peptide of < 0.3 nmol/l. Subjects with a history or presence of cancer and/or cardiac diseases, proliferative retinopathy or maculopathy and/or severe neuropathy were excluded. Subjects were also excluded if receiving current treatment with systemic (oral or intravenous [i.v.]) corticosteroids, monoamine oxidase inhibitors, systemic nonselective β-blockers, growth hormone, non-routine vitamins or herbal products. Individuals with recurrent severe hypoglycemia or hypoglycemic unawareness, or those who were pregnant, breast-feeding or intending to become pregnant were also excluded from participation.

2.3 Interventions and pharmacokinetic sampling

Eligible subjects were randomized to two periods of 8 days of once-daily dosing at one of three dose levels (low [0.4 U/kg], middle [0.6 U/kg] or high [0.8 U/kg]) and one of two treatment sequences (either IDeg followed by IGlar or IGlar followed by IDeg) according to a predefined randomization scheme. The two treatment periods were separated by a washout period of 7 – 21 days. IDeg and IGlar were administered as s.c. once-daily injections into a lifted skinfold on the anterior surface of the thigh. Dosing of trial product was performed at ~ 20.00 h each day by a person otherwise not involved in the study to keep the double-blind character of the study. During treatment periods, additional control of blood glucose levels was accomplished by bolus injections of insulin aspart, which were injected s.c. into a lifted skinfold of the lower abdominal wall. Adjustment of the bolus doses were supervised by the investigator on a daily basis and based on daily blood glucose readings. Bolus insulin was not administered for 10 h before and throughout the glucose clamp. In the current study, both investigator and subjects were blinded to trial treatment.

Blood samples for assessing the SS pharmacokinetics (serum IDeg and IGlar concentrations) were evaluated at one dosing interval (24 h) on days 6 and 8. On day 8, blood samples for determination of serum IDeg and IGlar concentration were additionally obtained at 30, 36, 48, 72, 96 and 120 h post-dose in order to investigate the terminal phase. From termination of the glucose clamp at 42 h, subjects resumed their usual insulin treatment with the exception that IDet and IGlar were not allowed until the last pharmacokinetic blood sample had been taken. Serum IDeg concentrations were measured using a validated specific sandwich enzyme-linked immunosorbent assay [11]. Serum IGlar concentrations were measured using a validated IGlar-specific luminescent oxygen channeling immunoassay that captures both intact IGlar and the glargine metabolites (metabolite 1 [M1] and metabolite 2 [M2]), thereby measuring all biologically active IGlar.

2.4 Pharmacodynamic measurements (clamp procedure)

At SS, immediately following the last dose of each treatment period, a 42-h euglycemic glucose clamp was performed by means of a Biostator® (glucose-controlled insulin infusion system; MTB Medizintechnik, Amstetten, Germany), as described previously [11]. Subjects were fasted (with no oral intake other than water) for 7 h prior to the clamp run-in period of 5 h. However, rapidly absorbable carbohydrates could be taken to prevent hypoglycemia prior to the clamp. Subjects experiencing hypoglycemia before a clamp were rescheduled. In brief, ~ 5 h before dosing of trial product, subjects received a variable i.v. infusion of human insulin (15 IU Actrapid®, 100 IU/ml in 49 ml saline and 1 ml of subject's blood) or glucose (20% glucose in water) to obtain a blood glucose clamp target level of 5.5 mmol/l (100 mg/dl).

After dosing, the i.v. insulin infusion (if any) was decreased gradually and stopped completely when blood glucose had decreased by 0.3 mmol/l (5 mg/dl); glucose infusion was then initiated to keep the glucose concentration constant at the glucose clamp target of 5.5 mmol/l (100 mg/dl). The clamp continued for 42-h post-dosing of trial product but was terminated earlier if the blood glucose exceeded 13.9 mmol/l (250 mg/ml) without any glucose having been administered for at least 30 min. During the entire clamp procedure, subjects remained fasting (with no oral intake other than water) and stayed in a supine or semi-supine position.

2.5 Assessments

The objective of this trial was to characterize the pharmacokinetic and pharmacodynamic properties of IDeg as compared to IGlar over a range of three clinically relevant doses (0.4, 0.6 and 0.8 U/kg) during one 24-h dosing interval (tau [τ]) to reflect clinical dosing frequency at SS in subjects with T1DM. Assessments were based on the pharmacokinetic dose–concentration relationship, the distribution and fluctuation of pharmacokinetic exposure, the terminal half-life, the pharmacodynamic dose–response relationship and the distribution and fluctuation in glucose-lowering effect. Safety assessments included adverse events (AEs), physical examination, clinical laboratory safety variables and hypoglycemic episodes (defined as 'confirmed' when they were either 'severe' as defined by the American Diabetes Association [12] or verified by a plasma glucose concentration < 3.1 mmol/l [56 mg/dl]).

2.6 Data and statistical analyses

The pharmacokinetic dose-proportionality was evaluated for the end points $AUC_{\tau,SS}$ and $C_{max,SS}$ using a linear model on log-transformed pharmacokinetic data, with period and log-dose level as fixed effects. Distribution of exposure over a 24-h dosing interval for IDeg and IGlar was quantified by estimating the ratio of AUC for the first 12-h interval versus the AUC for the entire 24-h interval (a 50:50 split: $AUC_{0-12\ h,SS}/AUC_{\tau,SS}$). Fluctuation of pharmacokinetic exposure over 24 h was quantified as the relative fluctuation of insulin concentration ($AUCF\%_{\tau,SS}$). This ratio estimates how much an individual's insulin concentration deviates from his or her mean concentration over 24 h (i.e., the average areas above and below the average concentration). Terminal half-life ($t_{½,SS}$) for IDeg and IGlar was estimated from the individual log-concentration-time profiles following the last dose of IDeg and IGlar.

The quality of the conducted clamps was assessed as previously described [13] from dosing until 24 h or until the last infusion of glucose whichever came first. Smoothing of glucose infusion rate (GIR) profiles was achieved with the Loess smoothing technique, using a fixed smoothing parameter of 0.15 and sampling with 5-min intervals. $AUC_{GIR,\tau,SS}$ was calculated as the area under the smoothed GIR profile using the linear trapezoidal technique on interpolated points. The log-transformed $AUC_{GIR,\tau,SS}$ was analyzed using an analysis of variance method with treatment and treatment period as fixed factors, subject as a random effect and an error variance depending on treatment.

The pharmacodynamic dose–response relationship for IDeg was evaluated for the end point $AUC_{GIR,\tau,SS}$ using a linear model on log-transformed pharmacodynamic data, with period and an interaction term between treatment and dose level as fixed effects and subject as random effect. Distribution of glucose-lowering effect over a 24-h dosing interval was assessed by estimating the ratio between the AUC for sub-areas under the GIR curves (50:50 split and 25:25:25:25 split) versus the total AUC for the complete 24-h dosing interval ($AUC_{GIR,\tau,SS}$) (GIR 50:50 split: $AUC_{GIR,0-12\ h,SS}/AUC_{GIR,\tau,SS}$ and GIR 25:25:25:25 split, proportion of GIR AUC; $AUC_{GIR,0-6\ h,SS}/AUC_{GIR,\tau,SS}$; $AUC_{GIR,6-12\ h,SS}/AUC_{GIR,\tau,SS}$; $AUC_{GIR,12-18\ h,SS}/AUC_{GIR,\tau,SS}$; $AUC_{GIR,18-24\ h,SS}/AUC_{GIR,\tau,SS}$). Fluctuation of glucose-lowering effect over 24 h was quantified using the mean fluctuation in GIR profile ($AUCF_{GIR,\tau,SS}$: estimates how much an individual's GIR profile deviates from his or her mean GIR over 24 h).

3. Results

3.1 Subjects

Of the 77 subjects screened, 66 were randomized (22 at each dose level) to one of the three fixed doses (0.4, 0.6, 0.8 U/kg) for both IDeg and IGlar (**Figure 1**). All 66 subjects were exposed to at least one drug administration; two subjects withdrew from the trial due to serious AEs. Both subjects were withdrawn during the first treatment period (treatment sequence: IGlar 0.4 U/kg then IDeg 0.4 U/kg and IGlar 0.6 U/kg then IDeg 0.6 U/kg, respectively), and thus did not receive treatment with IDeg. Baseline characteristics of the subjects included within this trial are shown in **Table 1**.

3.2 SS pharmacokinetics

The mean 24-h SS serum insulin concentration–time profiles at the three dose levels for both IDeg and IGlar are shown in **Figure 2**. It is worthy to note that it is not possible to compare the absolute serum concentrations of IDeg and IGlar due to the affinity of IDeg for albumin (see Section 4, for details). Total exposure and maximum concentration of IDeg increased proportionally with increasing dose, with estimated log-dose slopes of 0.99 $[0.76; 1.22]_{95\%CI}$ for $AUC_{\tau,SS}$ (**Figure 3**) and 0.85 $[0.63; 1.08]_{95\%CI}$ for $C_{max,SS}$. For IGlar, estimated log-dose slopes were 0.99 $[0.76; 1.21]_{95\%CI}$ for $AUC_{\tau,SS}$ and 1.01 $[0.77; 1.26]_{95\%CI}$ for $C_{max,SS}$. Exposure to IDeg was close to evenly distributed over the first and second 12 h for all three doses ($AUC_{0-12h,SS}/AUC_{\tau,SS}$ 52 – 54%). For IGlar, ~ 60% of exposure occurred in the first 12 h after dosing (**Table 2**). Individual serum insulin levels fluctuated less around the individual mean levels with IDeg (13 – 14%) than with IGlar (21 – 24%) (**Table 2**). The mean $t_{½,SS}$ for IDeg and IGlar estimated for each dose level and across the three dose levels

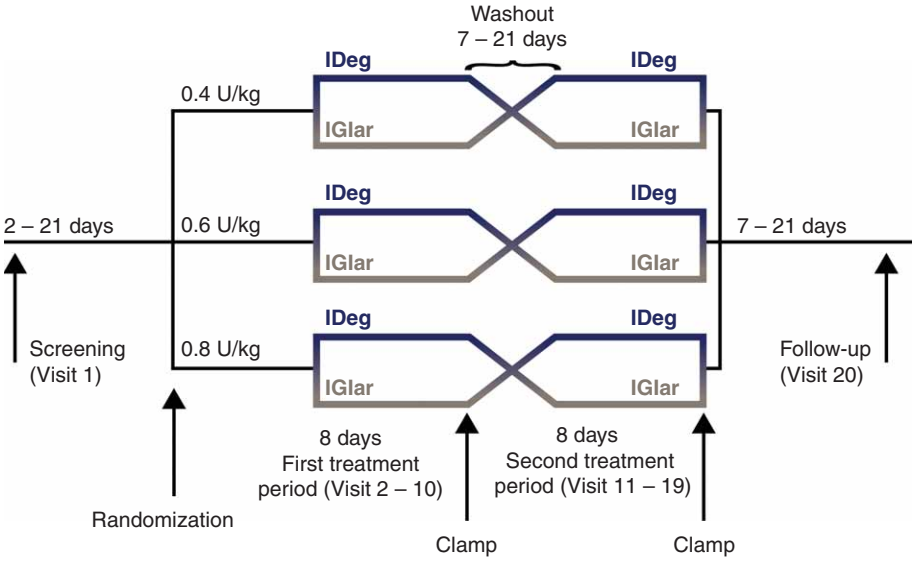

Figure 1. Flow diagram showing the trial design. The trial consisted of a screening visit (Visit 1) followed by two treatment periods (Visits 2 – 10 and Visits 11 – 19) and a follow-up visit (Visit 20). There was 2 – 21 days between the screening visit and the first treatment period. Each treatment period had a duration of 13 days, consisting of 8 days with once-daily dosing with IDeg or IGlar followed by a period of 5 days with blood sampling, until 120 h after last dosing (including a glucose clamp period of 42 h). The two treatment periods were separated by a washout period (7 – 21 days) during which the subjects resumed their normal insulin treatment.

IDeg: Insulin degludec; IGlar: Insulin glargine.

Table 1. Baseline characteristics.

Key demographics	Dose level			Total (n = 66)
	0.4 U/kg (n = 22)	0.6 U/kg (n = 22)	0.8 U/kg (n = 22)	
Sex, male/female	18/4	20/2	17/5	55/11
Age, years	36.0 (± 11.3)	36.8 (± 9.9)	38.0 (± 10.3)	36.9 (± 10.4)
BMI, kg/m^2	24.9 (± 2.4)	25.2 (± 2.5)	24.7 (± 2.5)	24.9 (± 2.4)
Duration of diabetes, years	15.8 (± 9.3)	18.8 (± 8.7)	18.2 (± 10.4)	17.6 (± 9.5)
HbA_{1C}, % [min; max] (± 1.2)	8.4 [5.7 – 10.0]	7.9 [6.6 – 10.0] (± 1.0)	8.0 [7.0 – 9.5] (± 0.8)	8.1 [5.7 – 10.0] (± 1.0)
C-peptide, nmol/l	0.03 (± 0.04)	0.01 (± 0.01)	0.03 (± 0.06)	0.02 (± 0.04)

Data are arithmetic mean (± SD) unless otherwise indicated.

BMI: Body mass index; HbA_{1c}: Glycated hemoglobin.

are shown in **Table 3**. The terminal $t_{½,SS}$ across the three dose levels was twice as long for IDeg compared to IGlar (25.4 vs 12.1 h).

3.3 SS pharmacodynamics

Clamp quality was high and comparable between treatment groups. The mean (± SD) difference of all paired blood glucose measurements of the Biostator versus the glucose analyzer reference method ('trueness') was 0.6 ± 1.6 mg/dl for IDeg and 0.9 ± 1.7 mg/dl for IGlar. The mean absolute difference ('accuracy') was 6.3 ± 1.4 and 6.6 ± 1.7%. The precision (i.e., the coefficient of variation in the blood glucose levels) was 6.8 ± 2.6 and 6.6 ± 1.7%. The mean difference between the Biostator blood glucose level and the target blood glucose level ('control deviation') was 0.4 ± 0.8 and 0.7 ± 1.2 mg/dl.

The total glucose-lowering effect of IDeg ($AUC_{GIR,\tau,SS}$) increased proportionally with increasing dose, with an estimated log-dose slope of 1.35 $[0.94; 1.75]_{95\%CI}$ (not assessed for IGlar). The mean 24-h SS GIR profiles of IDeg were flatter and more stable during one dosing interval for the three dose levels compared to that of IGlar (**Figures 4** and **5**). The glucose-lowering effect was similar over the first and second 12 h with IDeg for all three dose levels ($AUC_{GIR,0-12h,SS}/AUC_{GIR,\tau,SS}$ ~ 50%). Approximately 60% of total glucose infusion occurred over the first 12 h with IGlar (**Table 2**). The glucose-lowering effect profile

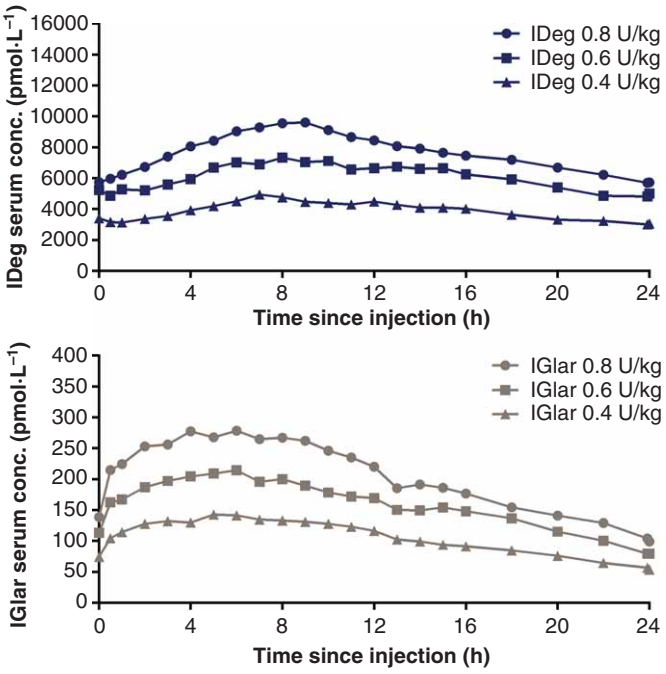

Figure 2. Pharmacokinetic profiles: 24 h insulin concentration–time profiles – IDeg and IGlar at steady state are shown. Please note that it is not possible to compare the absolute serum concentrations of IDeg and IGlar due to the affinity of IDeg for albumin (see Section 4, for details).
IDeg: Insulin degludec; IGlar: Insulin glargine.

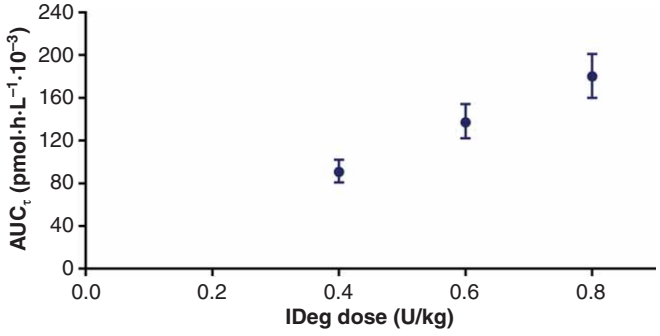

Figure 3. IDeg dose–concentration relationship at steady state is shown. Data are least square means and 95% CIs.
IDeg: Insulin degludec.

for IDeg compared with IGlar was further analyzed by plotting AUC_{GIR} for each of the four 6-h intervals as a percentage of $AUC_{GIR,\tau,SS}$ (**Figure 5**). The total glucose-lowering effect was more evenly distributed across a 24-h dosing interval with IDeg than IGlar, with more of the effect of IGlar occurring during the first 12 – 18 h after dosing (**Figure 5**). Accordingly, the relative fluctuation in GIR ($AUCF_{GIR,\tau,SS}$) was lower for IDeg (0.25 – 0.38 mg/[kg·min]) than for IGlar (0.39 – 0.73 mg/[kg·min]) at steady state (**Table 2**).

3.4 Safety

Both treatments were well tolerated, and no unexpected safety concerns were identified. Overall, 11 AEs were reported in 7 subjects treated with IDeg and 23 AEs were reported in 13 subjects treated with IGlar. Two serious AEs (intraspinal abscess and gastrointestinal hemorrhage), not judged to be related to study drug, were reported in subjects treated with IGlar. A total of 82 confirmed treatment-emergent hypoglycemic episodes were reported in 40 subjects treated with IDeg, compared to 102 reported in 40 subjects treated with IGlar; one episode was evaluated as severe (0.4 U/kg IGlar group).

4. Discussion

The narrow therapeutic window of insulin, combined with the variability of absorption and the relatively short

Table 2. Pharmacokinetic and pharmacodynamic parameters.

	IDeg			IGlar		
	0.4 U/kg	**0.6 U/kg**	**0.8 U/kg**	**0.4 U/kg**	**0.6 U/kg**	**0.8 U/kg**
Pharmacokinetics						
50:50 split*						
$AUC_{0–12h,SS}/AUC_{\tau,SS}$ (%)	53	52	54	60	59	61
Fluctuation*						
$AUCF\%_{\tau,SS}$	14	13	14	22	21	24
Pharmacodynamics						
50:50 split*						
$AUC_{GIR,0–12h,SS}/AUC_{GIR,\tau,SS}$ (%)	51	51	49	60	59	58
Fluctuation*						
$AUCF_{GIR,\tau,SS}$ (mg/kg•min)	0.25	0.37	0.38	0.39	0.54	0.73

Pharmacokinetics: $AUC_{0\ –\ 12\ h,SS}$, area under the insulin curve from 0 – 12 h at steady state; $AUC_{\tau,SS}$: total area under the insulin curve over a 24-h dosing interval at steady state; $AUCF\%_{\tau,SS}$: fluctuation of exposure over 24 h at steady state $(AUC_{[above\ Cmean]} + AUC_{[below\ Cmean]})/AUC_{\tau}$.

Pharmacodynamics: $AUC_{GIR,0\ –\ 12\ h,SS}$, area under the GIR curve from 0 – 12 h at steady state; $AUC_{GIR,\tau,SS}$: total area under the GIR curve over a 24-h dosing interval at steady state; $AUCF_{GIR,\tau,SS}$: $(AUC_{[above\ GIRmean]} + AUC_{[below\ GIRmean]})/24$.

*****Data are geometric means.

GIR: Glucose infusion rate; IDeg: Insulin degludec; IGlar: Insulin glargine; SS: Steady state; τ: Dosing interval.

Table 3. Half-life for IDeg and IGlar at steady state.

	IDeg			IGlar		
	0.4 U/kg	**0.6 U/kg**	**0.8 U/kg**	**0.4 U/kg**	**0.6 U/kg**	**0.8 U/kg**
Half-life (h)	25.9	27.0	23.6	11.5	12.9	11.9
Mean (h)		25.4			12.1	

Data are harmonic means.

IDeg: Insulin degludec; IGlar: Insulin glargine.

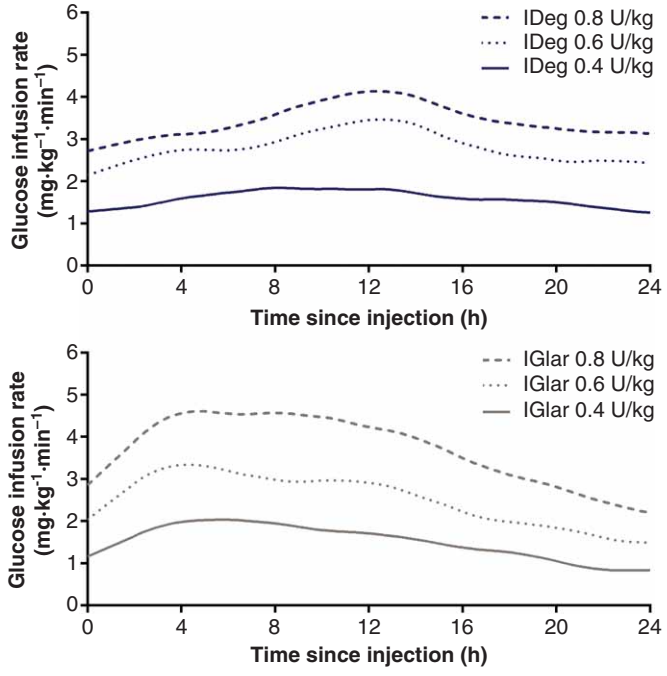

Figure 4. Pharmacodynamic profiles: 24 h GIR profiles – IDeg and IGlar at steady state are shown.

GIR: Glucose infusion rate; IDeg: Insulin degludec; IGlar: Insulin glargine.

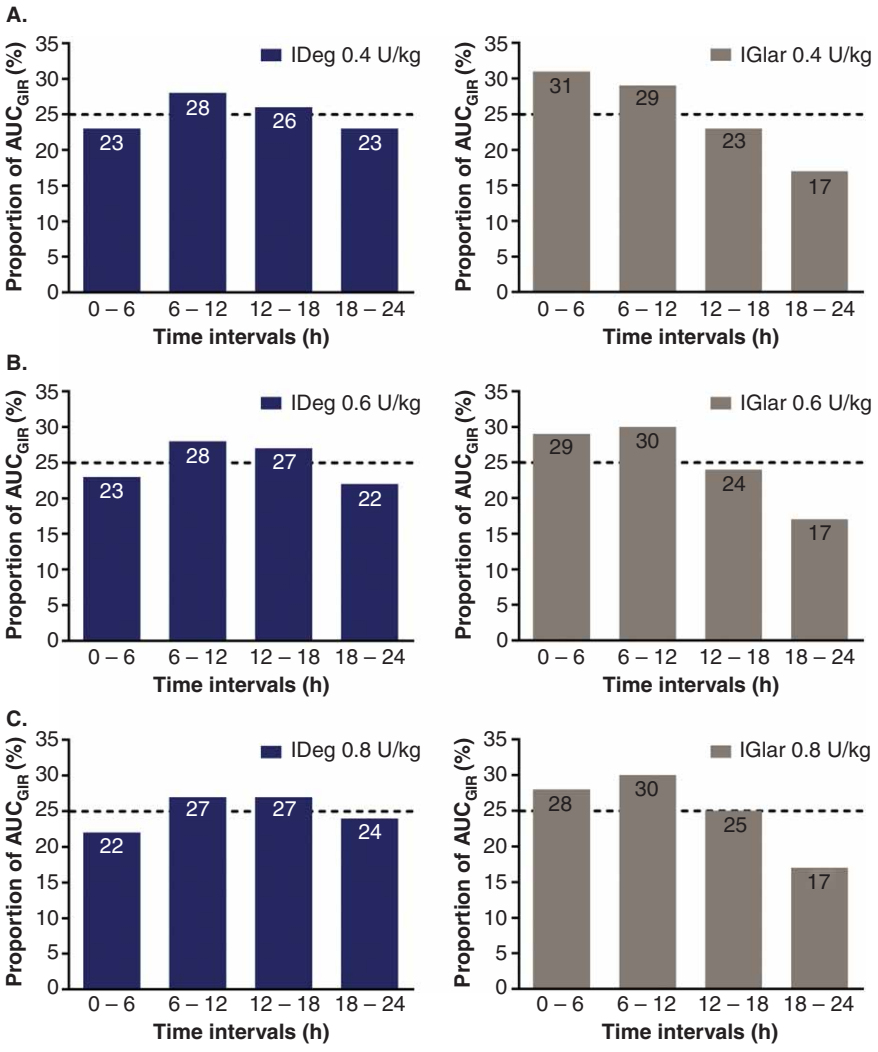

Figure 5. Distribution of glucose-lowering effect is shown for insulin degludec and insulin glargine at steady state at (A) 0.4 U/kg, **(B)** 0.6 U/kg and **(C)** 0.8 U/kg.
IDeg: Insulin degludec; IGlar: Insulin glargine.

pharmacokinetic half-lives of current basal insulin products often provide challenges to achieve both night-time and interprandial glycemic control with a low risk of hypoglycemia with once-daily dosing. This clinical trial evaluated the pharmacodynamic and pharmacokinetic properties of IDeg as compared to IGlar over a range of three clinically relevant doses during one 24-h dosing interval at SS in subjects with T1DM.

Assessment of the pharmacokinetic profiles showed that the estimated half-life was longer for IDeg compared to IGlar (25.4 vs 12.1 h) across all three dose levels. The twice longer half-life of IDeg compared to IGlar demonstrated in this study reflects the slow and sustained absorption of IDeg from the site of administration into the circulation. The slow absorption of IDeg has also been shown in subjects with T2DM, where the half-life of IDeg was ~ 25 h [11].

An important prerequisite for a flatter and more stable glucose-lowering effect profile within a dosing interval is that a once-daily basal insulin has an action profile that extends substantially beyond 24 h. This is because, under SS conditions, the overlapping action of several injections decreases the peak-to-trough ratio [5]. Therefore, the long half-life of IDeg would be expected to lead to less fluctuation in insulin levels and glucose-lowering effect across the 24-h dosing interval [14,15], as shown in the present study.

A lower variability in the glucose-lowering effect of IDeg versus IGlar across the 24-h dosing interval as well as from day to day should translate into reductions in the rate of confirmed hypoglycemia [10]. Accordingly, data from three long-term studies with IDeg in subjects on basal bolus therapy with T1DM [16] and T2DM [17,18] have shown lower rates of nocturnal hypoglycemia than with IGlar. Furthermore, a

recent meta-analysis of seven clinical trials demonstrated that the rate of nocturnal confirmed hypoglycemic episodes in subjects with T1DM was significantly lower with IDeg compared with IGlar during maintenance treatment [19].

This study examined the pharmacokinetic and pharmacodynamic properties of IDeg as compared to IGlar under SS conditions, which is considered the relevant setting for basal insulin showing overlapping action of consecutive injections. Compared to healthy subjects and subjects with T2DM, the lack of endogenous insulin production or acquired insulin resistance in the T1DM population facilitated the study of clinically relevant pharmacodynamic responses at therapeutic dose levels at SS [20]. The inclusion of IGlar as an active comparator in this study allowed for comparison to be made in pharmacokinetic and pharmacodynamic assessments of IDeg with a long-acting insulin product.

A limitation of this and all glucose clamp studies is the experimental setup as the euglycemic glucose clamp procedure is innately distinct from the clinical environment. As such, this artificial model can make it difficult to translate study findings to clinical reality. Furthermore, the use of fixed doses (0.4, 0.6 or 0.8 U/kg) of insulin independent of the subjects' individual insulin requirement does not reflect clinical practice as insulin should always be titrated and adjusted in line with each subjects' insulin requirements. However, using a broad dose range to establish dose–concentration and dose–response relationships is a regulatory requirement in a study of this nature. Still, the rate of hypoglycemic events that occurred in this trial may be artificially high due to the study design, and the lack of individual basal insulin dose adjustments. As is also the case for IDet, a major fraction of IDeg in the circulation is bound to albumin, while only a minor fraction is freely circulating [9]. The assay used to measure the concentration of IDeg in serum detects the total IDeg concentration, that is, the sum of the free fraction and the albumin-bound fraction. Thus, compared to insulin that does not bind to albumin in the circulation, measured serum IDeg concentrations are high. However, only the free fraction of IDeg is available to the insulin receptor. Importantly, the fact that the total glucose-lowering effect of IDeg and IGlar are comparable (as seen in the current study) suggests that the overall number of insulin molecules available to and being internalized by the insulin receptor over one dosing interval is comparable for IDeg and IGlar.

In conclusion, IDeg has a half-life of ~ 25 h, twice as long as that observed for IGlar, and has a pharmacokinetic exposure that is more stable and evenly distributed across a 24-h dosing interval compared to IGlar. The pharmacokinetic profile translated into a glucose-lowering effect profile that was flatter and more stable across a 24-h dosing interval for IDeg than for IGlar. The pharmacokinetic and pharmacodynamic properties of IDeg reported in this study clarify the findings from Phase III clinical trials: IDeg may help achieve improved nighttime and interprandial glycemic control, provide a lower risk of hypoglycemia than other forms of treatment and allow some degree of flexibility in the timing of administration [19].

Declaration of interest

This study was funded by Novo Nordisk A/S. Physician time was paid for at normal rates. Data processing and statistical analysis were performed by Novo Nordisk A/S, who also coordinated the study. T Heise is a shareholder of Profil, Neuss, Germany. Within the past year, this institution received research funds from Adocia, Becton Dickinson, Biocon, Boehringer Ingelheim, Bristol-Myers Squibb, Dance Pharmaceuticals, Evolva, Hoffmann La-Roche, Johnson & Johnson, Eli Lilly, Marvel, Novartis, Novo Nordisk, Sanofi and Servier. In addition, T Heise received speaker honoraria from Eli Lilly and Novo Nordisk, received travel grants from Novo Nordisk and is a member of advisory panels for Novo Nordisk. SG Bøttcher is an employee of Novo Nordisk A/S. H Haahr is an employee and shareholder of Novo Nordisk A/S. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Medical writing support was provided by Edward Kitchen and Dr Nason Ma'ani, apothecom scopemedical Ltd, London, UK, and by Carsten Roepstorff, Larix A/S, Copenhagen, Denmark, funded by Novo Nordisk.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Ashwell SG, Gebbie J, Home PD. Twice-daily compared with once-daily insulin glargine in people with Type 1 diabetes using meal-time insulin aspart. Diabet Med 2006;23:879–86
2. Albright ES, Desmond R, Bell DS. Efficacy of conversion from bedtime NPH insulin injection to once- or twice-daily injections of insulin glargine in type 1 diabetic patients using basal/bolus therapy. Diabetes Care 2004;27:632–3
3. DeVries JH. To: Scholtz HE, Pretorius SG, Wessels DH, Becker RHA. Pharmacokinetic and glucodynamic variability: assessment of insulin glargine, NPH insulin and insulin ultralente in healthy volunteers using a euglycaemic clamp technique. Diabetologia 2006;49:1125–6
4. Heise T, Pieber TR. Towards peakless, reproducible and long-acting insulins. An assessment of the basal analogues based on isoglycaemic clamp studies. Diabetes Obes Metab 2007;9:648–59
5. Heise T, Korsatko S, Nosek L, et al. Steady state is reached within 2-3 days of once-daily administration of degludec, a basal insulin with an ultralong duration of action. J Diabetes 2015. [Epub ahead of print]
6. Heise T, Nosek L, Rønn BB, et al. Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. Diabetes 2004;53:1614–20
7. Klein O, Lynge J, Endahl L, et al. Albumin-bound basal insulin analogues (insulin detemir and NN344): comparable time-action profiles but less variability than insulin glargine in type 2 diabetes. Diabetes Obes Metab 2007;9:290–9
8. Kurtzhals P, Heise T, Strauss HM, et al. Multi-hexamer formation is the underlying basis for the ultra-long glucose-lowering effect of insulin degludec. Diabetologia 2011;54:S426
9. Jonassen I, Havelund S, Hoeg-Jensen T, et al. Design of the novel protraction mechanism of insulin degludec, an ultra-long-acting basal insulin. Pharm Res 2012;29:2104–14

• **This article reports a series of investigative studies in the process of designing the protraction mechanism of insulin degludec.**

10. Heise T, Hermanski L, Nosek L, et al. Insulin degludec: four times lower pharmacodynamic variability than insulin glargine under steady-state conditions in type 1 diabetes. Diabetes Obes Metab 2012;14:859–64
11. Heise T, Nosek L, Bøttcher SG, et al. Ultra-long-acting insulin degludec has a flat and stable glucose-lowering effect in type 2 diabetes. Diabetes Obes Metab 2012;14:944–50
12. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care 2013;36:1384–95
13. Benesch C, Heise T, Klein O, et al. How to assess the quality of glucose clamps? Evaluation of clamps performed with ClampArt, a novel automated clamp device. J Diabetes Sci Technol 2015. [Epub ahead of print]
14. Meneghini L, Atkin SL, Gough SC, et al. NN1250-3668 (BEGIN FLEX) Trial Investigators. The efficacy and safety of insulin degludec given in variable once-daily dosing intervals compared with insulin glargine and insulin degludec dosed at the same time daily: a 26-week, randomized, open-label, parallel-group, treat-to-target trial in individuals with type 2 diabetes. Diabetes Care 2013;36:858–64
15. Heise T, Meneghini LF. Insulin staking versus therapeutic accumulation: understanding the differences. Endocr Pract 2014;20:75–83

•• **This review carefully explains the concept of appropriate accumulation of long-acting insulin formulations dosed to steady state.**

16. Heller S, Buse J, Fisher M, et al. BEGIN Basal-Bolus Type 1 Trial Investigators. Insulin degludec, an ultra-long acting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet 2012;379:1489–97

• **This article presents the results of a pivotal Phase III trial comparing efficacy and safety of insulin degludec and insulin glargine in subjects with type 1 diabetes.**

17. Garber AJ, King AB, Del Prato S, et al. NN1250-3582 (BEGIN BB T2D) Trial Investigators. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet 2012;379:1498–507

• **This article presents the results of a pivotal Phase III trial comparing efficacy and safety of insulin degludec and insulin glargine in subjects with type 2 diabetes.**

18. Zinman B, Philis-Tsimikas A, Cariou B, et al. NN1250-3579 (BEGIN Once Long) Trial Investigators. Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). Diabetes Care 2012;35:2464–71
19. Ratner RE, Gough SC, Mathieu C, et al. Hypoglycaemia risk with insulin degludec compared with insulin glargine in type 2 and type 1 diabetes: a pre-planned meta-analysis of phase 3 trials. Diabetes Obes Metab 2013;15:175–84

•• **This article presents the results of a pre-planned meta-analysis of Phase III trials to compare hypoglycemia risk between insulin degludec and insulin glargine.**

20. Owens DR, Bolli GB. Beyond the era of NPH insulin–long-acting insulin analogs: chemistry, comparative pharmacology, and clinical application. Diabetes Technol Ther 2008;10:333–49

Affiliation

Tim Heise[†1], Ulrike Hövelmann[1], Leszek Nosek[1], Lidia Hermanski[1], Susanne G Bøttcher[2] & Hanne Haahr[3]
[†]Author for correspondence
[1]Profil Institut für Stoffwechselforschung GmbH, Hellersbergstr. 9, D-41460 Neuss, Germany
Tel: + 49 2131 4018 411;
E-mail: Tim.Heise@profil.com
[2]Novo Nordisk A/S, Biostatistics, Søborg, Denmark
[3]Novo Nordisk A/S, Clinical Pharmacology, Søborg, Denmark