Ultra-long-acting Insulin Degludec Has a Flat and Stable Glucose-lowering Effect

1. **Leszek Nosek**
Neuss, Germany
2. **Tim Heise**
Neuss, Germany
3. **Susanne G Bøttcher**
Søborg, Denmark
4. **Hanne Hastrup**
Søborg, Denmark
5. **Hanne Haahr**
Søborg, Denmark

Abstract

Insulin degludec (IDeg) is a new-generation, ultra-long-acting basal insulin that forms soluble multi-hexamers upon subcutaneous injection, resulting in a depot from which IDeg is continuously and slowly absorbed into the circulation.

In this double-blind, two-period, crossover trial, we investigated the dose-response relationship of three doses of IDeg (0.4, 0.6, and 0.8 U/kg) at steady state (SS) in people with type 2 diabetes. Participants (insulin-treated people with type 2 diabetes without concomitant oral anti-diabetic agents, n=49; mean age, 58.7 years; BMI, 29.6 kg/m²; A1C, 7.6%; duration of diabetes, 14.1 years) were given IDeg once daily for 6 days, with a washout period of 13–21 days between treatments. Following dosing on Day 6, subjects underwent a euglycemic glucose clamp (Biostator; clamp blood glucose level: 90 mg/dL). Pharmacokinetic samples were taken up to 120 h after the last injection of IDeg.

For all dose levels, mean 24 h glucose infusion rate (GIR) profiles were flat and stable (Figure 1). Total glucose-lowering effect ($AUC_{GIR,total,SS}$) increased linearly with increasing dose. Over 24 h, the glucose-lowering effect of IDeg was evenly distributed between the first and second 12 h for all 3 dose levels ($AUC_{GIR,0-12h,SS}$ / $AUC_{GIR,total,SS}$ = 0.5). The blood glucose levels of all participants stayed very close to the clamp level until the end of the experiment (mean blood glucose levels in the last 10min of a 24-h dosing interval were 90–92 mg/dL for all IDeg doses). The terminal half-life estimated across the three dose levels after the last dose was 25.1 h. IDeg was well tolerated and no safety concerns were identified. In conclusion, IDeg has a flat and stable blood glucose-lowering effect, and a duration of action beyond 24 h in people with type 2 diabetes.

Introduction

- With the existing long-acting insulin analogs, some subjects with diabetes need twice-daily treatment to cover basal insulin requirements. Consequently, there is a need for an ultra-long-acting insulin suitable for once-daily use in all subjects.
- The ideal properties of a basal insulin would be to provide continuous, flat, and stable insulin replacement over an entire 24 h period.
- Insulin degludec (IDeg) is a new-generation, ultra-long-acting basal insulin developed for once-daily use in all subjects with diabetes.
- Upon subcutaneous injection, IDeg forms soluble multi-hexamers, resulting in a depot from which IDeg is continuously and slowly absorbed into the circulation. This gives rise to an ultra-long glucose-lowering effect that exceeds 40 h at clinically relevant doses (see Poster 32-LB).

Aims

- This trial was designed to evaluate the pharmacodynamic dose-response relationship of IDeg 100 U/ml within a therapeutically relevant dose range in subjects with type 2 diabetes.
- Here we present an evaluation of the glucose-lowering effect during a dosing interval of 24 h at steady state in subjects with type 2 diabetes.

This trial was registered at ClinicalTrials.gov, ID number: NCT01154881.

Methods

- This was a randomized, double-blind, two-period, incomplete block crossover, multiple-dose trial with 49 insulin-treated subjects with type 2 diabetes (without concomitant oral anti-diabetic agents) (Table 1).
- Subjects were randomly allocated to two of four possible IDeg treatments (IDeg 100 U/ml - 0.4, 0.6, 0.8 U/kg; or IDeg 200 U/ml - 0.6 U/kg) in a pre-determined sequence.
- Each treatment was administered once daily for 6 days, with a wash-out period of 13–21 days between treatment.
- Subjects underwent a 26-h euglycemic clamp (Biostator; clamp blood glucose level: 90 mg/dl (5 mmol/l)) after the last dose at the end of each treatment period (Day 6).
- Blood samples for assessment of steady-state pharmacokinetics were drawn for 120 h after the last dose.

Table 1: Baseline characteristics

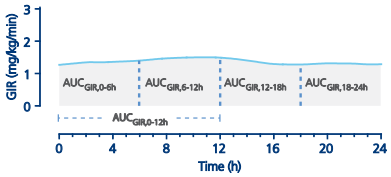
Key demographics	Total (n=49)
Sex (male/female)	**40/9**
Race (% White)	**100**
Age (years)	**59** (±7.4)
Body mass index (kg/m²)	**29.6** (±3.0)
Duration of type 2 diabetes (years)	**14** (±7.4)
Baseline A1C (%)	**7.6** (±0.9)
Fasting C-peptide serum (nmol/l)	**0.44** (±0.25)

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

Statistical analyses

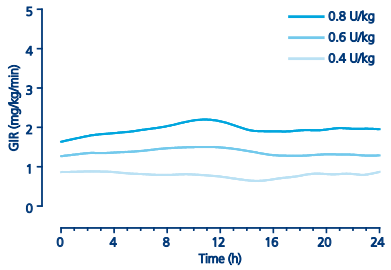
- The dose-response relationship of the total area under the glucose infusion rate (GIR) curve over a 24 h dosing interval at steady state ($AUC_{GIR,\tau}$) was investigated using a linear mixed model on log-transformed GIR data with period, dose, and dose squared as fixed effects depending on trial product, subject as a random effect, and an error variance depending on trial product and dose level.
- Distribution of the glucose-lowering effect over 24h dosing interval was quantified by estimating the ratio between the AUC for sub-areas under the GIR profiles (either 50:50 split and 25:25:25:25 split) versus the total AUC for the entire 24 h dosing interval ($AUC_{GIR,\tau}$) (Figure 1).
- Terminal half-life ($t_{½}$), was estimated from the individual log-insulin profiles.

Figure 1: Illustration of sub-areas under GIR profiles (using either a 50:50 split or a 25:25:25:25 split)



Results

Figure 2: Mean glucose infusion rate profiles over 24 h at steady state



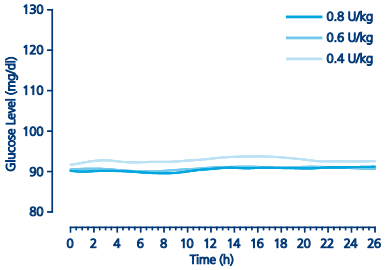
- The total glucose-lowering effect over 24 h ($AUC_{GIR,\tau}$ IDeg 100 U/ml) increased linearily with increasing dose.
- The glucose-lowering effect of IDeg was flat and stable at all three dose levels (Figure 2).

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
50:50 split			
$AUC_{GIR,0-12h}$ / $AUC_{GIR,\tau}$ (%)	48.9	53.0	50.4
25:25:25:25 split			
$AUC_{GIR,0-6h}$ / $AUC_{GIR,\tau}$ (%)	27.4	26.8	24.2
$AUC_{GIR,6-12h}$ / $AUC_{GIR,\tau}$ (%)	21.5	26.3	26.2
$AUC_{GIR,12-18h}$ / $AUC_{GIR,\tau}$ (%)	19.8	22.7	23.9
$AUC_{GIR,18-24h}$ / $AUC_{GIR,\tau}$ (%)	31.3	24.3	25.8

Numbers are arithmetic means. $AUC_{GIR,x-y h}$: area under the GIR curve for a specified time interval after injection. $AUC_{GIR,\tau}$:total area under the GIR curve over a 24 h dosing interval at steady state.

Figure 3: Mean 26 h blood glucose profiles at steady state



- Blood glucose levels did not reach end of action of 150 mg/dl (8.3 mmol/l) within the 26-h clamp for any subject, and mean blood glucose levels stayed at the clamp target level until end of the clamp (Figure 3). Thus, duration of action was beyond 26 h in all subjects at all three dose levels.

Table 3: Terminal half-life of IDeg

Estimate	IDeg dose		
	0.4 U/kg	0.6 U/kg	0.8 U/kg
$t_{½}$ (h)	24.6	24.4	26.8
Mean $t_{½}$ (h)		25.1	

Data are harmonic means.

- The total glucose-lowering effect of IDeg was evenly distributed over 24 h for all three dose levels, both when looking at the first and second 12 h ($AUC_{GIR,0-12h}$ / $AUC_{GIR,\tau}$ ~ 0.50:50%), and over 6-h intervals (Table 2).
- The terminal half-life was ~25 h across all three IDeg dose levels (Table 3).
- IDeg was well tolerated and no safety concerns were identified.

Conclusions

These results show that at steady state:

- IDeg has a flat and stable glucose-lowering effect. The glucose-lowering effect of IDeg is consistent and evenly distributed over the 24 h period.
- Blood glucose remained at the clamp target level until end of the clamp and end of action was not reached in any subject.
- These results confirm that IDeg has a duration of action beyond 26 h in subjects with type 2 diabetes.

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