Steady state is reached within two to three days of once-daily administration of ultra-long-acting insulin degludec

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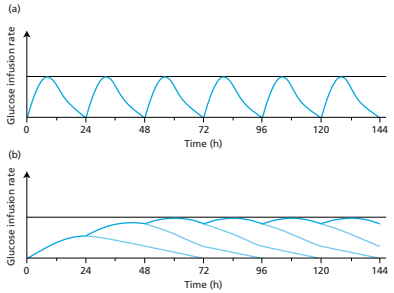
Introduction

- The objective of basal insulin therapy is to ensure continuous insulin coverage throughout the 24 hours of the day.
- When used in once-daily regimens, insulins with a duration of action of ≤24 hours are characterised by action profiles with periods of low action rising to a peak/plateau followed by a decline (Figure 1a).
- An important prerequisite for a flatter and more stable glucose-lowering effect at steady state is that the once-daily basal insulin has an action profile that extends substantially beyond 24 hours. This is because, under steady-state conditions, the overlapping action of several injections will decrease the peak-to-trough ratio (Figure 1b).
- Insulin degludec (IDeg) is a new basal insulin that has a half-life of ~25 hours and a consistent glucose-lowering effect of >42 hours at clinically relevant doses.

Figure 1 Conceptual model showing action profiles with once-daily dosing.



- When initiating and titrating any insulin, it is important from a clinical perpective to know the time it takes for the insulin to reach steady-state plasma concentrations (i.e., when the amount of insulin elimination is equal to the amount of insulin absorption) because this helps to determine the optimal interval for dose titration.
- Here we present an evaluation of the time taken for IDeg to reach steady state following once-daily dosing in subjects with type 1 (T1D) and type 2 (T2D) diabetes mellitus.

Methods

- We used data from three PK/PD trials (two trials in subjects with T1D and one trial in subjects with T2D) to analyse time to steady state.
- In these randomised double-blind trials, subjects with T1D and T2D (Table 1 and Table 2, respectively) received once-daily subcutaneous injections of IDeg (100 U/mL) at 0.4 U/kg for 12 days (T1D – Trial 1), 0.4, 0.6 or 0.8 U/kg for 8 days (T1D – Trial 2) or 0.4, 0.6 or 0.8 U/kg for 6 days (T2D – Trial 3).
- Blood samples were taken before each dosing to determine the serum IDeg trough concentration on each day relative to the plateau serum IDeg trough concentration measured during the last days of the treatment period.

Table 1 Baseline characteristics – subjects with T1D.

	Trial 1 (n=27)	Trial 2 (n=66)
Sex (male/female)	23/4	55/11
Age (years)	40.3 (±10.7)	36.9 (±10.4)
Body mass index (kg/m²)	24.6 (±2.4)	24.9 (±2.4)
Duration of diabetes (years)	20.2 (±12.9)	17.6 (±9.5)
Baseline HbA_{1c} (%)	7.8 (±1.1)	8.1 (±1.0)
Fasting C-peptide serum (nmol/L)	0.02 (±0.03)	0.02 (±0.04)

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

- The 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.[1]

Table 2 Baseline characteristics – subjects with T2D.

	Trial 3 (n=49)
Sex (male/female)	40/9
Age (years)	58.7 (±7.4)
Body mass index (kg/m²)	29.6 (±3.0)
Duration of diabetes (years)	14.1 (±7.4)
Baseline HbA_{1c} (%)	7.6 (±0.9)
Fasting C-peptide serum (nmol/L)	0.44 (±0.25)

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

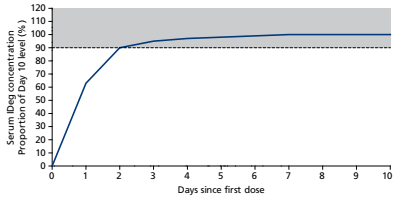
Statistical analyses

- Log-transformed serum IDeg concentrations were analysed separately for each trial using an ANOVA model with dose level (except Trial 1) and time from first dose as fixed effects and subject as a random effect. Contrasts for each time point relative to the last time point were estimated.

Results

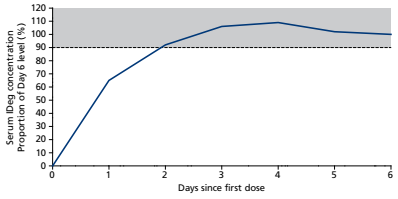
- Steady state was reached after 2–3 days of IDeg dosing (Figures 2–4), regardless of type of diabetes. This was the case for all subjects.
- The time to reach steady state was independent of IDeg dose for both Trial 2 (p=0.51) and Trial 3 (p=0.75). In Trial 1 only a single IDeg dose level was tested.
- At steady state, total exposure (serum concentration) of IDeg was unchanged from day to day, as shown by the similar day-to-day serum IDeg trough concentrations.

Figure 2 Relative serum IDeg trough concentrations during initiation of once-daily dosing in subjects with T1D (Trial 1).



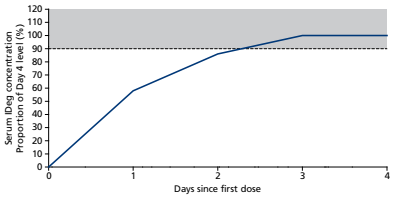
Values are estimated ratios relative to Day 10.

Figure 3 Relative serum IDeg trough concentrations during initiation of once-daily dosing in subjects with T1D (Trial 2).



Values are estimated ratios relative to Day 6.

Figure 4 Relative serum IDeg trough concentrations during initiation of once-daily dosing in subjects with T2D (Trial 3).



Values are estimated ratios relative to Day 4.

References

1. Rowland M and Tozer TN. *Clinical Pharmacokinetics and Pharmacodynamics – Concepts and Applications*. 4th ed. Lippincott Williams & Wilkins. 2011.

Conclusions

- IDeg reached steady-state within 2–3 days of subcutaneous administration in all study participants with type 1 or type 2 diabetes.
- At steady state, serum IDeg concentrations were unchanged from day to day.

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