Steady state is reached within two to three days of once-daily administration of degludec, a basal insulin with an ultra-long duration of action

Short title

Insulin degludec: steady state within 2–3 days

Tim HEISE,[1] Stefan KORSATKO,[2] Leszek NOSEK,[1] Hans Veit COESTER,[1] Sigrid DELLER,[2] Carsten ROEPSTORFF,[3] Stine SEGEL,[4] Rahul KAPUR,[3] Hanne HAAHR,[3] Marcus HOMPESCH,[5]

[1]Profil, Neuss, Germany

[2]Medical University of Graz, Graz, Austria

[3]Novo Nordisk A/S, Søborg

[4]Novo Nordisk A/S, Aalborg

[5]Profil Institute for Clinical Research, Chula Vista, CA, USA

Corresponding author

Tim Heise, Profil Institute for Metabolic Research, Hellersbergstr. 9, D-41460 Neuss, Germany

Tel: +49 2131 4018 411

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/1753-0407.12266

This article is protected by copyright. All rights reserved.

Accepted Article

Email: Tim.Heise@profil.com

Word count: 2271

Number of tables and figures: 2 tables and 2 figures

Abstract

Background: Various factors influence the pharmacokinetic and pharmacodynamic properties of insulin analogs. The aim of this study was to determine time to steady state of insulin degludec (IDeg), a basal insulin analog with an ultra-long duration of action, after once-daily subcutaneous administration in subjects of varying age, diabetes type and ethnicity.

Methods: Time to steady state was analyzed in 195 subjects across five phase I, randomized, single-center, double-blind studies – three in subjects with type 1 diabetes (T1DM), including one in elderly subjects and two in subjects with type 2 diabetes (T2DM), including one study with African-American and Hispanic/Latino subpopulations. Subjects received once-daily subcutaneous injections of IDeg (100 U/mL) at dose levels of 0.4–0.8 U/kg for 6–12 days. Time to clinical steady state was measured from first dose until serum IDeg trough concentration exceeded 90% of the final plateau level. IDeg concentrations were log-transformed and analyzed using a mixed-effects model with time from first dose and dose level (where applicable) as fixed effects, and subject as a random effect.

Results: Steady-state serum concentrations of IDeg were reached after 2–3 days of IDeg in all subjects. In trials with multiple dose levels, time to steady state was independent of dose level in T1DM (p=0.51) and T2DM (p=0.75).

Conclusions: Serum concentrations of IDeg reached steady state within 2–3 days of once-daily subcutaneous administration in all subjects with T1DM or T2DM, including

This article is protected by copyright. All rights reserved.

Accepted Article

elderly and African-American and Hispanic/Latino subjects. At steady state, serum IDeg concentrations were unchanged from day to day.

The significant finding (s) of the study:

This study demonstrated that serum concentrations of IDeg reached steady state in subjects of different race, ethnicity, age or type of diabetes within 2–3 days of once-daily subcutaneous administration. Once at steady state, serum IDeg concentrations remain unchanged.

This study adds:

This study is the first to show that time to steady state of IDeg appears similar irrespective of race, ethnicity, age or type of diabetes.

Keywords: basal insulin, diabetes, pharmacokinetics, steady state

Accepted Article

This article is protected by copyright. All rights reserved.

Accepted Article

Introduction

The objective of basal insulin therapy is to ensure continuous insulin coverage throughout the 24 hours of the day. However, when used in once-daily regimens, insulins with duration of action of ≤24 hours are characterized by action profiles with periods of low glucose-lowering effect that rise to a peak/plateau at some point during the day, to be followed by a decline towards the end of the day (Figure 1a), sometimes resulting in a requirement for twice-daily injections to cover basal insulin needs, particularly in subjects with type 1 diabetes [1–2]. In addition, some insulins have a mode of protraction based on formation of microprecipitates or crystals after injection that must redissolve before absorption [3], an inherently variable process that may also contribute to variation in glucose-lowering effect [4,5].

An important prerequisite for a flatter and more stable glucose-lowering effect is that the once-daily basal insulin has an action profile that extends substantially beyond 24 hours. With this longer half-life, exposure increases over the first days of treatment, before approaching a plateau, where overall absorption and elimination of the drug is in dynamic equilibrium and no further increase in insulin serum concentration occurs (steady state). Under steady-state conditions, the overlapping action of several injections will decrease the peak-to-trough ratio (Figure 1b), thereby reducing variability in glucose-lowering effect.

Insulin degludec (IDeg) is a novel basal insulin analog developed for once-daily subcutaneous administration in subjects with type 1 diabetes [6] or type 2 diabetes [7]. IDeg has a distinct absorption mechanism [8] such that upon subcutaneous injection it forms multi-hexamers that result in a soluble depot in subcutaneous tissue from which monomers gradually separate and are absorbed into the circulation [9].

This article is protected by copyright. All rights reserved.

This mechanism of prolonged and stable absorption leads to a half-life of ~25 hours, twice that of insulin glargine [10], a flat and consistent glucose-lowering effect [11] and an ultra-long duration of action; of over 42 hours [9,12]. Various factors can influence the pharmacokinetic and pharmacodynamic properties of insulins and thus the time taken to reach steady state, with potential implications in titration methods. The aim of this analysis was to determine the duration and consistency of time to steady-state serum concentration of IDeg following once-daily subcutaneous dosing in subjects of varying age and diabetes type, and in subjects of African-American race or of Hispanic/Latino ethnicity.

Methods

Study populations

This study is based on data collated from 195 subjects from five clinical trials (for two of the trials, a subset of the full trial population is included, as separate trials already report on the other study populations; see Table 1). Three trials were in subjects with type 1 diabetes, including one in the elderly, and two trials were in subjects with type 2 diabetes, including one in subjects of African-American race or of Hispanic/Latino ethnicity. All participants received insulin treatment prior to enrollment and all had a baseline HbA_{1c} of ≤10% (≤86 mmol/mol).

Key inclusion criteria for all subjects with type 1 diabetes were a BMI of 18–28 kg/m^2 and fasting C-peptide <0.3 nmol/L. Key inclusion criteria for all subjects with type 2 diabetes included BMI ≤40 kg/m^2 (35 kg/m^2 for Trial 1987) and fasting C-peptide <1.0 nmol/L. General exclusion criteria included known allergy to investigational products and receipt of investigational products <3 months prior to trials. Individuals with clinically significant concomitant diseases, a history of recurrent severe hypoglycemia

This article is protected by copyright. All rights reserved.

Accepted Article

or hypoglycemic unawareness, or those who were pregnant or breastfeeding, were also excluded from participation.

Study design and pharmacokinetic sampling

This is a *post hoc* analysis based on data extracted from the five individual clinical trials, all investigating the pharmacokinetic and pharmacodynamic properties of IDeg (Table 1). All studies included were phase I, randomized, single-center, double-blind trials. In each trial, the protocol, protocol amendments, consent form and subject information sheets were reviewed and approved by appropriate local institutional review boards prior to trial initiation. All studies were performed in accordance with the Declaration of Helsinki together with all amendments that were current at the time of trial initiation.

Subjects received once-daily subcutaneous injections of IDeg (100 U/mL) at 0.4 U/kg for 12 days (adults, type 1 diabetes, Trial 1991), 0.4, 0.6 or 0.8 U/kg for 8 days (adults, type 1 diabetes, Trial 1993), 0.4 U/kg for 6 days (elderly, type 1 diabetes, Trial 1994), 0.4, 0.6 or 0.8 U/kg for 6 days (Caucasian adults, type 2 diabetes, Trial 1987), or 0.6 U/kg for 6 days (African-American or Hispanic/Latino adults, type 2 diabetes, Trial 3762). Before receiving the first IDeg dose, subjects underwent a washout period during which 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 prior to the first trial drug dose was used for calculation of the daily dose and this was used for all subsequent doses. During the treatment periods blood glucose levels were controlled by additional bolus injections of insulin aspart (IAsp), supervised by the investigator on a daily basis.

Blood samples were taken before each dosing to determine the serum IDeg trough concentration on each day.

This article is protected by copyright. All rights reserved.

Accepted Article

Serum IDeg concentrations were measured using a specific enzyme-linked immunosorbent assay (ELISA).

Data and statistical analyses

The time to clinical steady state was defined as the time from first dose until serum IDeg trough concentrations exceeded 90% of the final plateau level [13].

Serum IDeg trough concentrations were log-transformed and analyzed for each trial using a mixed effects model with time from first dose as a fixed effect and subject as a random effect. In Trials 1993 and 1987 dose level was also included as a fixed effect and the interaction between time from first dose versus dose level was initially included as a fixed effect, but removed if non-significant. In Trial 3762 the analyses were performed separately for each sub-population. Contrasts for each time-point relative to the time-point for the last concentration taken outside clamp conditions were estimated. One subject in Trial 1994 was exposed to IDeg but withdrew on Day 5 of IDeg treatment; data from this subject are therefore included in baseline characteristics but not in the relevant steady-state figure.

Results

Subjects

A total of 195 subjects from the five trials were included in time to steady-state calculations (Table 1). Baseline characteristics of the subjects are summarized in Table 2.

Steady state

In all studies investigated, IDeg reached steady state after 2−3 days of IDeg dosing (Figure 2a–f), regardless of type of diabetes. In the two studies that investigated

This article is protected by copyright. All rights reserved.

Accepted Article

more than one dose level of IDeg, the interaction between time from first dose to steady state versus dose level was not significant (Trial 1993 [p=0.51] and Trial 1987 [p=0.75]), indicating that the time to reach steady state was independent of IDeg dose level. At steady state, the serum concentration of IDeg was similar from day to day (Figure 2). In all studies, IDeg was well tolerated and no unexpected safety issues were raised.

Discussion

After repeated doses, IDeg trough concentration levels (i.e. measured immediately before the next IDeg dose) increased before reaching a plateau or steady state after 2–3 days at which time the exposure to IDeg remained similar from day to day. At steady state, rate of absorption (rate with which IDeg is absorbed into the circulation), and rate of elimination (rate with which IDeg is eliminated) are in dynamic equilibrium and there will not be any further increase in insulin concentration levels. Steady state is then maintained with continued dosing of IDeg until modifications are made to insulin dose level. When an insulin is at steady state it should exhibit a constant metabolic effect over time [14]. In theory, for all practical purposes, clinical steady state can be considered to be reached in approximately three half-lives, i.e. when 90% of the theoretical steady-state level is reached [13], although this can occur more rapidly [15].

In the studies analyzed here, covering 195 patients with type 1 diabetes or type 2 diabetes from five clinical trials (for two of the trials, a subset of the full trial population is included), IDeg consistently reached steady state within 2–3 days of once-daily subcutaneous administration. The time to reach steady state was similar in elderly, African-American, Hispanic/Latino sub-populations and in Caucasian

This article is protected by copyright. All rights reserved.

Accepted Article

subjects with type 1 or type 2 diabetes. The half-life of IDeg was dose level independent in the investigated range; consequently, the time to reach steady state concentration was also independent of dose level. Furthermore, at steady state, IDeg concentrations were unchanged from day to day and no further increase of IDeg serum concentration was observed. It should be noted that IDeg is not unique among long-acting diabetes treatments in requiring several days to achieve steady state. Similar observations have been made in cases such as pioglitazone (4–7 days to reach steady state) [16] or sitagliptin (≤7 days to reach steady state) [17], where following progressively increased exposure in the first few days a steady state condition is reached at which point rates of absorption and elimination are in equilibrium.

Steady state was reached within 3 days in all subjects. This is faster than anticipated based on theoretical calculations which would predict that 90% of plateau levels are reached within three to four half-lives (i.e. in approximately 3 to 4 days for IDeg with a half-life of around 24 hours). One possible reason for IDeg reaching steady-state faster than predicted may stem from its relatively low insulin receptor affinity compared to human insulin [18] and its strong albumin binding [8]. Intravenous kinetic studies showed that the clearance and volume of distribution of insulin analogs decreased with increasing albumin binding affinity [19].

As for all currently available basal insulins injected subcutaneously, the major mechanism for protracted action of IDeg is achieved primarily through slow absorption into the systemic circulation, thus the half-life is dependent on the rate of absorption rather than on elimination (flip-flop kinetics). Nevertheless, the relatively high albumin affinity may lead to some retention of IDeg in the circulation and as the definition for steady-state is based on the trough plasma levels, this could then

This article is protected by copyright. All rights reserved.

Accepted Article

accelerate the achievement of steady state. This time to steady state for IDeg is in line with that observed by Evans et al for drugs that follow first-order kinetics (i.e. a constant fraction of the drug in the body is eliminated for each unit of time), in which concentrations reach to within 98% of final after approximately three half-lives [15].

The time to reach steady state is clinically relevant for IDeg, as the pharmacodynamic profile seen after single-dose administration differs to that at steady state [11]. The time to steady state was consistent across populations, indicating the half-life of IDeg remained unaffected in the sub-populations reported here. The long half-life implies an extended duration of action and therefore a decrease in the peak-to-trough ratio for glucose-lowering effect when dosed once daily (Figure 1b).

It should be noted that due to this time to achieve steady state, IDeg should not be titrated daily as the full pharmacodynamic effect of IDeg would only be discernible once steady state has been reached. Furthermore, in the few days prior to achieving steady state, hyperglycemia may not be completely corrected.

Large scale clinical trials have demonstrated IDeg provides both effective glycemic control and greater flexibility in dosing than insulin glargine once steady state has been reached [20]. Furthermore, pooled data from clinical studies of IDeg in type 1 and type 2 diabetes show the rate of confirmed hypoglycemia (including nocturnal confirmed hypoglycemia) is reduced with IDeg compared with insulin glargine [21]. Lower rates of nocturnal confirmed hypoglycemia have also been reported with use of IDeg compared with insulin glargine in elderly subjects [22]. The lower rates of hypoglycemia provide clinically relevant evidence that levels of IDeg do not accumulate once steady state is achieved.

Accepted Article

This article is protected by copyright. All rights reserved.

In conclusion, this study demonstrated that the time to reach a steady-state concentration of IDeg was consistently within 2–3 days across a range of patient populations, and serum IDeg concentrations at steady state were similar from day to day.

Acknowledgements

Medical writing assistance was provided by apothecom scopemedical, UK, funded by Novo Nordisk. This study was funded by Novo Nordisk, and presented as a poster at EASD 2012 (poster 909, HV Coester et al).

Tim Heise is the guarantor and all authors accept full responsibility for the contents of the article.

Disclosure

Tim Heise is shareholder of Profil, Neuss, Germany. Within the last 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, TH received speaker honoraria from Eli Lilly and Novo Nordisk, received travel grants from Novo Nordisk and is a member of advisory panels from Novo Nordisk.

Stefan Korsatko, Leszek Nosek, Hans Veit Coester and Sigrid Deller have no potential conflicts to declare.

Carsten Roepstorff, Stine Segel, Rahul Kapur and Hanne Haahr are employees and shareholders of Novo Nordisk.

This article is protected by copyright. All rights reserved.

Accepted Article

Marcus Hompesch has served on advisory panels for Boehringer Ingelheim and Hanmi Pharmaceuticals. He is an employee and shareholder of Profil, San Diego, US.

References

1. 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.
2. Devries JH. To: Scholtz HE, Pretorius SG, Wessels DH, Becker RHA (2005) pharmacokinetic and glucodynamic variability: assessment of insulin glargine, NPH insulin and insulin ultralente in healthy volunteers using a euglycaemic clamp technique. Diabetologia 48:1988–1995. Diabetologia 2006; **49**: 1125–6.
3. Berchtold T and Hilgenfeld R. Binding of phenol to R6 insulin hexamers. Biopolymers 1999; **51**: 165–72.
4. Heise T, Nosek L, Rønn BB, Endahl L, Heinemann L, Kapitza C, Draeger E. 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.
5. Heise T, Hermanski L, Nosek L, Feldman A, Rasmussen S, Haahr H. 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.
6. Heller S, Buse J, Fisher M, Garg S, Marre M, Merker L, Renard E, Russell-Jones D, Philotheou A, Francisco AM, Pei H, Bode B. Insulin degludec, an ultra-long-acting basal insulin, versus insulin glargine in basal-bolus treatment with

This article is protected by copyright. All rights reserved.

Accepted Article

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.

7. Garber AJ, King AB, Del Prato S, Sreenan S, Balci MK, Muñoz-Torres M, Rosenstock J, Endahl LA, Francisco AM, Hollander P. Insulin degludec, an ultra-long-acting 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**: 1498–1507.

8. Jonassen I, Havelund S, Hoeg-Jensen T, Steensgaard DB, Wahlund PO, Ribel U. Design of the novel protraction mechanism of insulin degludec, an ultra-long-acting basal insulin. Pharm Res 2012; **29**: 2104–14.

9. Kurtzhals P, Heise T, Strauss HM, Bøttcher SG, Granhall C, Haahr H, Jonassen I. Multi-hexamer formation is the underlying basis for the ultra-long glucose-lowering effect of insulin degludec. Diabetologia 2011; **54**(Suppl 1): S426.

10. Heise T, Hövelmann U, Nosek L, Bøttcher S, Granhall C, Haahr H. Insulin degludec has a two-fold longer half-life and a more consistent pharmacokinetic profile compared with insulin glargine (Abstract). Endocrine Abstracts 2012; **28**: P188.

11. Heise T, Nosek L, Bøttcher SG, Hastrup H, Haahr H. 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. Haahr H, Heise T. A review of the pharmacological properties of insulin degludec and their clinical relevance. Clinical Pharmacokinetics, in press

This article is protected by copyright. All rights reserved.

Accepted Article

13. Rowland M, Tozer T. Clinical Pharmacokinetics and Pharmacodynamics - Concepts and Applications. Philadelphia, PA: Lippincott, Williams & Wilkins. 2011.

14. Bott S, Tusek C, Jacobsen LV, Endahl L, Draeger E, Kapitza C, Heise T: Insulin detemir under steady-state conditions: no accumulation and constant metabolic effect over time with twice daily administration in subjects with Type 1 diabetes. Diabet Med 2006; **23**: 522–8.

15. Evans M, Schumm-Draeger PM, Vora J, King AB. A review of modern insulin analogue pharmacokinetic and pharmacodynamic profiles in type 2 diabetes: improvements and limitations. Diabetes Obes Metab 2011; **13**(8):677–84.

16. Actos tablets. Summary of Product Characteristics (eMC). 2013. Available from http://www.medicines.org.uk/emc/medicine/4236. Accessed 14 May 2014.

17. Januvia SmPC. 2013. Available from http://www.medicines.org.uk/emc/medicine/19609/SPC/JANUVIA+25mg%2c+50mg%2c+100mg+film-coated+tablets/. Accessed 14 May 2014.

18. Nishimura E, Sørensen A, Hansen BF, Stidsen C, Olsen GS, Schäffer L, Bonnesen C, Hegelund AC, Lundby A, Jonassen I. Insulin degludec is a new generation ultra-long acting basal insulin designed to maintain full metabolic effect while minimizing mitogenic potential. Diabetologia 2010; **53**: 388.

19. Havelund S, Plum A, Ribel U, Jonassen I, Vølund A, Markussen J, Kurtzhals P. The mechanism of protraction of insulin detemir, a long-acting, acylated analog of human insulin. Pharm Res 2004; **21**(8):1498–504.

20. Zinman B, Fulcher G, Rao PV, Thomas N, Endahl LA, Johansen T, Lindh R, Lewin A, Rosenstock J, Pinget M, Mathieu C. Insulin degludec, an ultra-long-

This article is protected by copyright. All rights reserved.

Accepted Article

acting basal insulin, once a day or three times a week versus insulin glargine once a day in patients with type 2 diabetes: a 16-week, randomised, open-label, phase 2 trial. Lancet 2011; **377**: 924–31.

21. Ratner R, Gough SC, Mathieu C, Del Prato S, Bode B, Mersebach H, Endahl L, Zinman B: 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.

22. Sorli C, Warren M, Oyer D, Mersebach H, Johansen T, Gough SC. Elderly patients with diabetes experience a lower rate of nocturnal hypoglycaemia with insulin degludec than with insulin glargine: A meta-analysis of phase IIIa trials. Drugs Aging. 2013; **30**(12): 1009–18.

23. Korsatko S, Deller S, Mader JK, Glettler K, Köhler G, Treiber G, Urschitz M, Wolf M, Hastrup H, Søndergaard F, Haahr H, Pieber TR. Ultra-long pharmacokinetic properties of insulin degludec are comparable in elderly subjects and younger adults with type 1 diabetes. Drugs Aging. 2014; **31**(1): 47–53.

24. Hompesch M, Morrow L, Watkins E, Roepstorff C, Thomsen HF, Haahr H. Pharmacokinetic and pharmacodynamic responses of insulin degludec in African American, white, and Hispanic/Latino patients with type 2 diabetes mellitus. Clin Ther. 2014; **36** :507-15

Accepted Article

This article is protected by copyright. All rights reserved.

Accepted Article

Figure captions

Figure 1 Conceptual model showing action profiles with once-daily dosing for (a) insulin with ≤24 h duration of action or (b) insulin with an ultra-long duration of action.

Figure 2 Relative serum insulin degludec (IDeg) trough concentrations during initiation of once-daily dosing in adult subjects with type 1 diabetes in (a) Trial 1991 [5] and (b) Trial 1993 [10], (c) elderly subjects with type 1 diabetes (Trial 1994) [23], (d) Caucasian subjects with type 2 diabetes (Trial 1987) [11], (e) African-American subjects with type 2 diabetes and (f) Hispanic/Latino subjects with type 2 diabetes (Trial 3762) [24].

This article is protected by copyright. All rights reserved.

Tables

Table 1. Study details

Study	Trial registration number	N	Type of diabetes	Patient type
1991 [5]	NCT00961324	27	Type 1 diabetes	Adult (18–65 years)
1993 [10]	NCT01114542	66	Type 1 diabetes	Adult (18–65 years)
1994 [23]	NCT00964418	14*	Type 1 diabetes	Elderly (≥65 years)
1987 [11]	NCT01154881	49	Type 2 diabetes	Caucasian (18–70 years)
3762 [24]	NCT01043510	40*	Type 2 diabetes	18 African American 22 Hispanic/Latino (18–70 years)

*Please note that only a subset of the full trial population is included for Trials 1994 (only elderly group included) and 3762 (only African American and Hispanic/Latino groups included); please refer to the individual trials for full study results

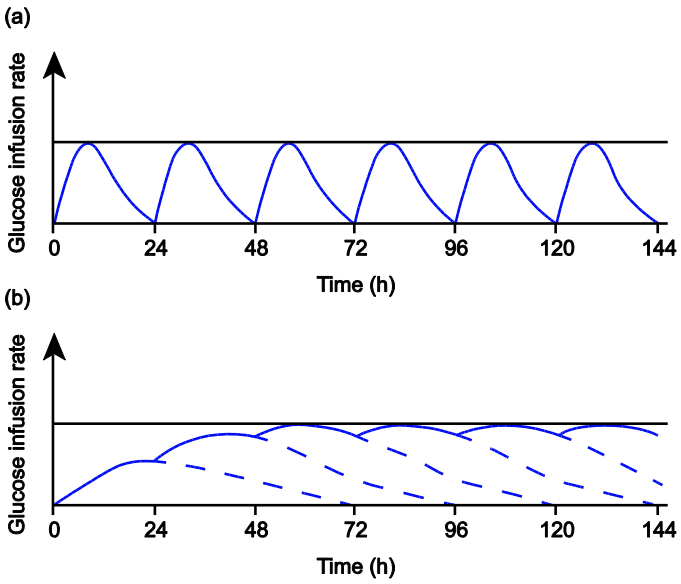
Accepted Article

This article is protected by copyright. All rights reserved.

Table 2 Baseline characteristics

Parameter	Type 1 diabetes			Type 2 diabetes		
	1991 (Adults) [5]	1993 (Adults) [10]	1994 (Elderly) [23]	1987 (Caucasian) [11]	3762 (African American) [24]	3762 (Hispanic/ Latino) [24]
Sex, male/female	23/4	55/11	6/8	40/9	11/7	13/9
Age (years)	40.3 (±10.7)	36.9 (±10.4)	67.8 (±3.2)	58.7 (±7.4)	48.9 (±8.4)	51.5 (±8.3)
Body mass index (kg/m^2)	24.6 (±2.4)	24.9 (±2.4)	26.2 (±1.5)	29.6 (±3.0)	35.3 (±3.7)	30.2 (±4.4)
Duration of diabetes (years)	20.2 (±12.9)	17.6 (±9.5)	40.6 (±16.3)	14.1 (±7.4)	9.3 (±3.0)	13.4 (±7.5)
Baseline HbA_{1c} (%)	7.8 (±1.1)	8.1 (±1.0)	7.7 (±0.6)	7.6 (±0.9)	8.3 (±1.4)	8.4 (±1.1)
Fasting C-peptide (nmol/L)	0.02 (±0.03)	0.02 (±0.04)	0.03 (±0.07)	0.44 (±0.25)	0.44 (±0.24)	0.49 (±0.26)

Data are arithmetic mean (±SD) unless otherwise indicated



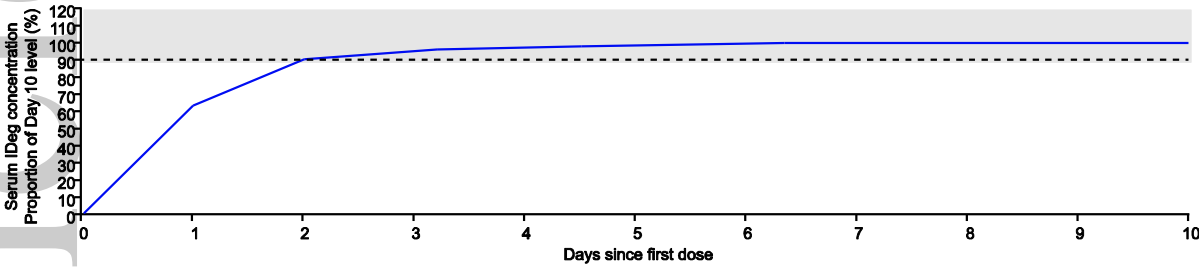
JDB_12266_F1

This article is protected by copyright. All rights reserved.

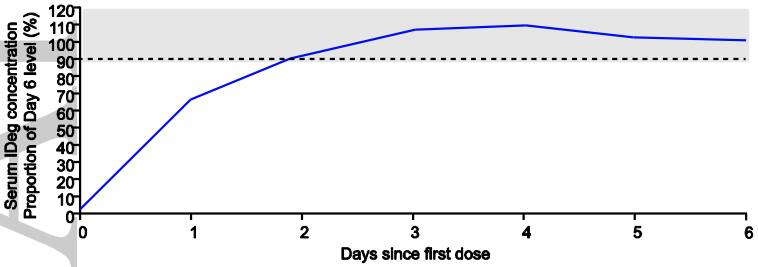
Accepted Article

Accepted Article

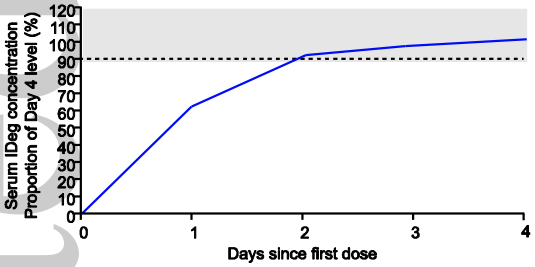
a) Younger adult subjects with type 1 diabetes (trial 1991)



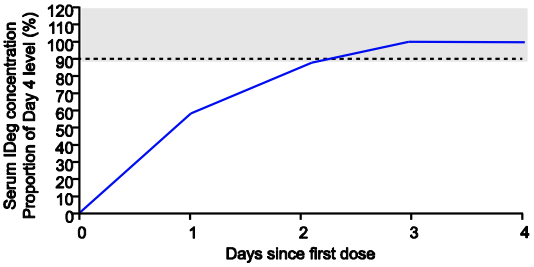
b) Younger adult subjects with type 1 diabetes (trial 1993)



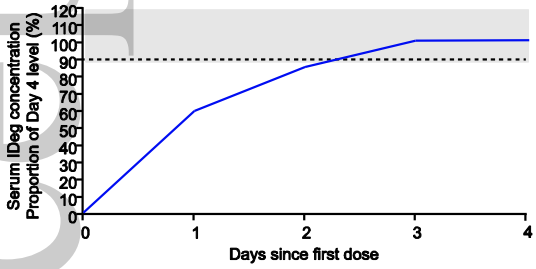
c) Elderly subjects with type 1 diabetes (trial 1994)



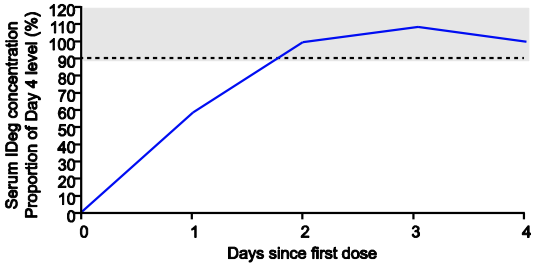
d) Caucasian subjects with type 2 diabetes (trial 1987)



e) African American subjects with type 2 diabetes (trial 3762)



f) Hispanic/Latino subjects with type 2 diabetes (trial 3762)



JDB_12266_F2

This article is protected by copyright. All rights reserved.