JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
CLINICAL TRIAL

Pharmacokinetic and pharmacodynamic properties of insulin degludec in Japanese patients with type 1 diabetes mellitus reflect similarities with Caucasian patients

Ippei Ikushima[1]*, Kohei Kaku[2], Koichi Hirao[3], Lars Bardtrum[4], Hanne Haahr[4]

[1]Department of Internal Medicine, SOUSEIKAI Global Clinical Research Center, Sumida Hospital, Tokyo, [2]Department of Internal Medicine, Kawasaki Medical School, Okayama, [3]Department of Internal Medicine, HEC Science Centre, Kanagawa, Japan, and [4]Novo Nordisk A/S, Søborg, Denmark

Keywords
Degludec, Insulin, Japanese

***Correspondence**
Ippei Ikushima
Tel.: +81-3-5608-7276
Fax: +81-3-5608-9536
E-mail address: ippei-ikushima@lta-med.com

J Diabetes Investig 2016; 7: 270–275

doi: 10.1111/jdi.12399

Clinical Trial Registry
ClinicalTrials.gov
NCT01135927

ABSTRACT

Introduction: The present study aimed to evaluate the pharmacokinetic and pharmacodynamic properties of insulin degludec (IDeg) in Japanese patients with type 1 diabetes.

Materials and Methods: This was a randomized, single-center, double-blind, two-period, crossover, multiple-dose trial. Patients were randomized into two treatment sequences, and received IDeg or insulin detemir for 6 days and a washout period (7–21 days) before switching treatment. Blood samples for pharmacokinetic measurements were obtained before each dose and up to 120 h after the last dose of each treatment period. Pharmacodynamic measurements were obtained using a 26-h euglycemic clamp procedure after the last dose of each treatment period.

Results: A total of 22 patients were randomized (14 men, 8 women; mean glycosylated hemoglobin at baseline of 7.5% [based on Japanese Diabetes Society value]). At steady state, total glucose-lowering effect (area under the glucose infusion rate [GIR] curve during one dosing interval [τ, 0–24 h] at steady state [$AUC_{GIR,\tau,SS}$]) was 1,446 mg/kg and total exposure (geometric mean) of IDeg ($AUC_{IDeg,\tau,SS}$) was 81,270 pmol h/L. Both the glucose-lowering effect and the exposure of IDeg were evenly distributed over the dosing interval, with AUC for the first 12-h intervals being approximately 50% of the total (geometric mean; $AUC_{GIR,0-12h,SS}/AUC_{GIR,\tau,SS}$ = 48%; $AUC_{IDeg,0-12h,SS}/AUC_{IDeg,\tau,SS}$ = 53%).

Conclusions: IDeg has a flat, consistent and ultra-long glucose-lowering effect that is evenly distributed across a 24-h interval and an ultra-long duration of action in Japanese patients with type 1 diabetes. These data support once-daily dosing of IDeg in all patients. Overall, the pharmacodynamic and pharmacokinetic end-points and safety observations are consistent with those previously reported in Caucasian patients.

INTRODUCTION

Basal insulin is an important element in the treatment of type 1 diabetes, and the use of long-acting insulin analogs as part of a basal–bolus injection regimen has resulted in significantly improved glycemic control. Reduced fasting plasma glucose and reduced all-day, severe and nocturnal hypoglycemic episodes were observed in several studies when insulin detemir (IDet) was compared with neutral protamine Hagedorn (NPH)[1,2]. Current basal insulins can be administered once daily; however, the duration of the glucose-lowering effect can vary between patients, resulting in a requirement for twice-daily injections in many patients, particularly in patients with type 1 diabetes[3,4].

Insulin degludec (IDeg) is a new-generation, ultra-long-acting insulin developed for once-daily administration with a distinct

Received 12 January 2015; revised 12 June 2015; accepted 8 July 2015

mechanism of protraction. On subcutaneous (SC) injection, IDeg forms multi-hexamers. These form a soluble depot in the SC tissue, from which monomers gradually separate at a consistent rate and are absorbed into the circulation[5,6]. This mechanism of absorption leads to flat, consistent, and long pharmacokinetic and pharmacodynamic profiles in Caucasian patients[5]. In addition, IDeg has low day-to-day variability in glucose-lowering effect and fourfold lower variability within patients compared with insulin glargine (IGlar) under steady-state conditions[7]. These findings, coupled with the duration of action of IDeg, which extends beyond 42 h in Caucasian patients, suggests that a delayed or missed injection might not compromise glycemic control to the same extent as currently available basal insulins[5,8]. Furthermore, throughout the clinical development program, IDeg was associated with significantly lower rates of nocturnal hypoglycemia at similar levels of glycemic control in type 1 diabetes compared with IGlar[9].

Thus far, no studies have reported on the pharmacokinetic and pharmacodynamic properties of IDeg in the Japanese population. As evidence suggests that drug responsiveness might be affected by race and ethnicity[10], it is important to investigate the pharmacological properties of a drug in patients from different race and ethnic backgrounds. Subsequently, the aim of the present study was to evaluate the pharmacokinetic and pharmacodynamic properties of IDeg in Japanese patients with type 1 diabetes. Furthermore, the data from the present study will allow for comparisons with results from an earlier study in Caucasian patients.

MATERIALS AND METHODS

Study Populations

Eligible participants were Japanese men and women aged 20–65 years (inclusive), with type 1 diabetes treated with insulin for ≥12 months with a daily basal insulin requirement of ≥0.3 (I)U/kg. Eligible participants had a body mass index (BMI) of 18.0–28.0 kg/m^2 (inclusive), with glycosylated hemoglobin (HbA_{1c}) levels ≤10.0% (values reported based on Japanese Diabetes Society value) and fasting C-peptide at baseline <0.3 nmol/L.

Exclusion criteria included: a history or presence of cancer or cardiovascular disease; supine blood pressure obtained at the screening visit outside the range of 90–140 mmHg for systolic blood pressure or 50–90 mmHg for diastolic blood pressure; proliferative retinopathy or maculopathy and/or severe neuropathy; recurrent severe hypoglycemia (more than one severe hypoglycemic event during the past 12 months) or hypoglycemic unawareness as judged by the investigator; or hospitalization for diabetic ketoacidosis during the previous 6 months. Patients who smoked more than five cigarettes or the equivalent per day were also excluded from this study.

Study Design

This was a single-center (Sumida Hospital, Tokyo, Japan), randomized, multiple-dose, double-blind, two-period, cross-over trial carried out in Japanese patients with type 1 diabetes (Clinical trials.gov number: NCT01135927). The protocol, any protocol amendments, the consent form, and the patient information sheet were reviewed and approved by a local institutional review board before trial initiation. Furthermore, the study was carried out in accordance with the Declaration of Helsinki and its amendments in force at the initiation of the trial, and in accordance with the Ministry of Health and Welfare (MHW) ordinance on good clinical practice (MHW Ordinance No. 28; 27 March 1997) and relevant applicable regulations. Patients were informed of the risks and benefits of the trial, and were informed that they could withdraw from the trial at any time for any reason. Consent was obtained in writing before any trial-related activities, and the investigator retained the consent forms.

Interventions and Pharmacokinetic Sampling

Individuals eligible for participation in the trial were randomized to one of the treatment sequences (either IDeg followed by IDet or IDet followed by IDeg). Both the investigator and the patients were blinded to trial treatment, and a person not otherwise involved in the trial prepared the doses. Before receiving the first dose, patients underwent a washout period during which their usual basal insulin was not taken for 48 h (for IDeg or IDet) or for at least 22 h (for NPH or other intermediate-acting insulin). Each treatment sequence included two treatment periods of 6 days of once-daily dosing of IDeg or IDet at 20.00 hours by a qualified person, followed by 5 days of pharmacokinetic blood sampling. To avoid any carry-over effect between treatment periods, the two treatment periods were separated by a washout period of 7–21 days. In addition, the patients were provided with NPH insulin (Novolin® N) to be used as basal insulin from clamp termination until the last blood sample for pharmacokinetic assessment had been taken. Patients were allowed to resume their usual insulin treatment after the last blood sample for pharmacokinetic assessment.

IDet was included primarily as a control (i.e., a comparator basal insulin analog to help evaluate treatment with IDeg) in the event that results for IDeg in Japanese patients differed from those reported previously in Caucasian patients[11]. As this was not observed, only results from IDeg treatment are reported herein. Plasma glucose level was controlled by additional bolus insulin (insulin aspart) during the treatment period (no bolus injections were administered for 10 h before dosing, and during the clamp procedure).

Blood samples for determination of serum IDeg concentration were obtained before administration of each dose. Immediately after the last dose, blood samples were taken frequently up to 36 h (at least every 1–2 h until 24 h post-dose and at 30- and 36-h time-points), with additional samples taken at 48, 72, 96 and 120 h post-dose.

Serum IDeg concentrations were measured using a specific sandwich enzyme-linked immunosorbent assay[7,12–14].

Pharmacodynamic Measurements (Clamp Procedure)

At steady state, immediately after the last dose in each treatment period, a 26-h euglycemic glucose clamp was carried out by means of a STG-22 (glucose-controlled insulin infusion system; Artificial Endocrine Pancreas; Nikkiso Co. Ltd., Tokyo, Japan).

The patients fasted (with no oral intake other than water) for 7 h before the clamp run-in period of 5 h. However, rapidly absorbable carbohydrates could be taken to prevent hypoglycemia before the clamp. Patients experiencing hypoglycemia before a clamp were rescheduled. In brief, approximately 5 h before dosing of the trial product, patients received a variable intravenous (i.v.) infusion of human insulin or 10% glucose solution to obtain a blood glucose clamp target 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 maintain the glucose concentration at the glucose clamp target of 5.5 mmol/L (100 mg/dL). The clamp continued for 26 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, patients remained fasting (with no oral intake other than water) and stayed in a supine or semi-supine position.

Statistical Analysis

The full analysis set comprised all randomized patients. Statistical analyses were carried out using SAS 9.1.3 software (SAS Institute Inc., Cary, NC, USA).

The primary end-point was the area under the glucose infusion rate (GIR) curve during one dosing interval (τ, 0–24 h) at steady state ($AUC_{GIR,\tau,SS}$) for IDeg treatment. Secondary pharmacodynamic end-points included duration of action and distribution of glucose-lowering effect across the dosing interval at steady state ($AUC_{GIR,0-12h,SS}/AUC_{GIR,\tau,SS}$). Secondary pharmacokinetic end-points included total exposure ($AUC_{IDeg,\tau,SS}$) and distribution of exposure over the dosing interval at steady state ($AUC_{IDeg,0-12h,SS}/AUC_{IDeg,\tau,SS}$). Safety end-points included adverse events (AEs), hypoglycemic episodes (hypoglycemic episodes were defined as 'confirmed' when they were either classified as 'severe' as defined by the American Diabetes Association[15] or 'minor' defined by plasma glucose <3.1 mmol/L [56 mg/dL], or verified by a full blood glucose <2.8 mmol/L [50 mg/dL]), local injection-site reactions, electrocardiogram, physical examination, vital signs and laboratory parameters.

$AUC_{GIR,\tau,SS}$ was calculated as the area under the smoothed GIR profile using the linear trapezoidal technique on interpolated points. Smoothing of GIR was achieved with the Loess smoothing technique, using a fixed smoothing parameter of 0.25 and sampling with 5-min intervals. The log-transformed $AUC_{GIR,\tau,SS}$ was analyzed using an analysis of variance method, with treatment and treatment period as fixed factors, and patient as a random effect. In order to account for potential heteroscedasticity, the error variance depended on the treatment.

Secondary pharmacodynamic end-points were derived from the individual GIR (smoothed) and blood glucose profiles at steady state. All other pharmacodynamic end-points were summarized using descriptive statistics. Distribution of exposure over a 24-h dosing interval at steady state was quantified by estimating the ratio between the AUC for the first 12-h interval over the total AUC for the entire 24-h dosing interval under the GIR ($AUC_{GIR,0-12h,SS}/AUC_{GIR,\tau,SS}$). In the present study, the duration of action was defined in accordance with previously published glucose clamp trials with IDeg[5] – that is, when blood glucose concentration consistently exceeded 8.3 mmol/L (150 mg/dL).

Secondary pharmacokinetic end-points were derived from insulin concentration–time curves at steady state. $AUC_{IDeg,\tau,SS}$ was calculated as the area under the insulin concentration–time profile using the linear trapezoidal technique based on observed values and actual measurement times between 0 and 24 h.

In *post-hoc* analyses, the time to clinical steady state for IDeg was defined as the time from first dose until serum IDeg trough concentrations exceeded 90% of the final plateau level[16].

RESULTS

Participants

A total of 24 patients were screened, 22 patients were randomized and exposed to at least one drug administration, and 21 patients completed the trial. One patient withdrew consent after visit 10, as he/she was not able to continue to visit the site because of an unintended change of his/her schedule (personal reasons). A total of 64% of patients were male (14/22), and the mean (standard deviation [SD]) age at baseline was 42 years (12 years). Mean (SD) BMI at baseline was 22.3 kg/m^2 (2.4 kg/m^2), and the mean (SD) duration of diabetes among patients was 18 years (11 years). Mean (SD) HbA_{1c} and fasting C-peptide concentration at baseline were 7.5% (1.1%) and 0.04 nmol/L (0.03 nmol/L), respectively.

Steady-State Pharmacodynamics

At steady state, the mean 24-h GIR profile of IDeg was flat and consistent (Figure 1). The mean $AUC_{GIR,0-12h,SS}/AUC_{GIR,\tau,SS}$ was 48% (Table 1), suggesting that the glucose-lowering effect of IDeg was relatively evenly distributed across the first and second 12 h of the 24-h dosing interval.

The total glucose-lowering effect of IDeg ($AUC_{GIR,\tau,SS}$; primary end-point) was 1,446 mg/kg (55%); geometric mean [coefficient of variation]).

Duration of Action at Steady State

Mean blood glucose profiles for IDeg were consistent throughout the 26-h clamp at a blood glucose level close to the clamp target of 5.5 mmol/L (100 mg/dL). The end of action (blood glucose above 8.3 mmol/L [150 mg/dL]) did not occur for any patients within the 26-h clamp period.

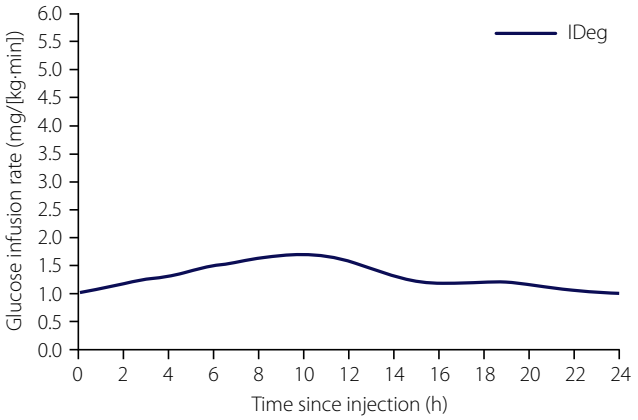

Figure 1 | Mean glucose infusion rate profiles for insulin degludec (IDeg) at steady state in Japanese patients with type 1 diabetes.

Table 1 | Pharmacodynamic end-points for insulin degludec at steady state in Japanese patients with type 1 diabetes

End-point	Japanese patients Mean (CV%)
$AUC_{GIR,\tau,SS}$ (mg/kg)	1,446 (55)
$AUC_{GIR,0–12h,SS}/AUC_{GIR,\tau,SS}$ (%)	48 (30)

Geometric mean presented. $AUC_{GIR,\tau,SS}$, area under the glucose infusion rate curve during one dosing interval (0–24 h as 'τ') at steady state; CV %, coefficient of variation in percent.

Steady-State Pharmacokinetics

IDeg trough levels (pharmacokinetic concentrations measured immediately before each dose) increased over the first days of treatment before reaching a plateau, and showed that steady state with IDeg was reached after 2–3 days of treatment in all patients, and was confirmed by *post-hoc* analyses (Table 2).

Total exposure with IDeg ($AUC_{IDeg,\tau,SS}$) was 81,270 pmol h/L and exposure to IDeg was evenly distributed across one dosing interval (Figure 2), with a mean $AUC_{IDeg,0–12h,SS}/AUC_{IDeg,\tau,SS}$ of 53% (Table 3). Mean pharmacokinetic 120-h profiles obtained after 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; data not shown).

Safety

IDeg was well tolerated, and no new safety issues were identified. Overall, three treatment-emergent AEs (other than hypoglycemia) were reported after treatment with IDeg. No serious AEs occurred; all AEs were mild in nature, and no injection-site reactions were recorded. A total of 93 confirmed treatment-emergent hypoglycemic episodes were reported in 13 patients for IDeg.

Table 2 | Relative trough concentrations of insulin degludec in Japanese patients with type 1 diabetes

Time after first dose	Estimated ratio† (relative to day 5)
Day 1	0.70
Day 2	0.98
Day 3	1.00
Day 4	0.98
Day 5	1.00

†Ratio was obtained by dividing serum concentrations of each day by the serum concentration on day 5.

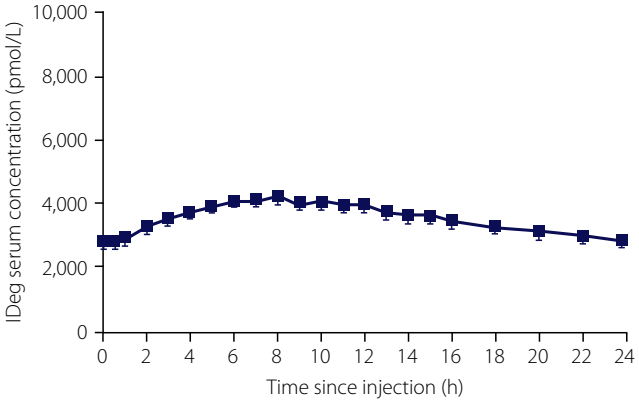

Figure 2 | Mean insulin degludec (IDeg) serum concentrations at steady state in Japanese patients with type 1 diabetes. Error bars represent the standard error of the mean.

Table 3 | Pharmacokinetic end-points for insulin degludec at steady state in Japanese patients with type 1 diabetes

End-point	Japanese patients Mean (CV%)
$AUC_{\tau,SS}$ (pmol h/L)	81,270 (28)
$AUC_{0–12h,SS}/AUC_{\tau,SS}$ (%)	53 (5.8)

Geometric mean presented. $AUC_{\tau,SS}$, area under the serum insulin concentration curve during one dosing interval (0–24 h as 'τ') at steady state; CV%, coefficient of variation in percent.

DISCUSSION

The present study examined the pharmacokinetic and pharmacodynamic properties of IDeg in Japanese patients with type 1 diabetes. Because of the ultra-long duration of action of IDeg, relevant pharmacodynamic investigations should be carried out at steady state, as this is a more clinically relevant context. IDeg has previously been shown to reach steady state after 2–3 days of treatment[17]; therefore, in this study, pharmacodynamic investigations were carried out on the sixth day of treatment.

The glucose-lowering effect of IDeg ($AUC_{GIR,\tau,SS}$ 1,446 mg/kg) was found to be evenly distributed throughout a 24-h dosing interval in Japanese patients ($AUC_{GIR,0–12h,SS}/AUC_{GIR,\tau,SS}$ 48%). Similar results were also reported in a recent study characterizing the pharmacodynamic response of IDeg during a 42-h euglycemic clamp in Caucasian patients with type 1 diabetes (at a dose of 0.4 U/kg: $AUC_{GIR,\tau,SS}$ 1,948 mg/kg, $AUC_{GIR,0–12h,SS}/AUC_{GIR,\tau,SS}$ 51%[11]; data on file).

Results from the current study also show that IDeg concentrations in Japanese patients 42 h after administration were similar to those reported in Caucasian patients with type 1 diabetes, and that IDeg was detectable in serum for at least 120 h after the last dose at steady state[5]. In addition, 24-h exposure to IDeg at a dose of 0.4 U/kg was similar in Japanese ($AUC_{\tau,SS}$ 81,270 pmol h/L) and Caucasian patients ($AUC_{\tau,SS}$ 82,612 pmol h/L)[18]. Furthermore, time to steady state for IDeg in Japanese patients was 2–3 days, which is consistent with that reported across patients of varying ethnic backgrounds[19].

As a clear relationship between exposure to IDeg and glucose-lowering effect has been shown, and as the long pharmacokinetic properties and GIR profiles of IDeg appear to be preserved in Japanese patients with type 1 diabetes, the duration of action of IDeg in this population would appear to be comparable with that observed in Caucasian patients with type 1 diabetes[5]. As expected, end of action of IDeg did not occur for any patient in the present study during the 26-h clamp period, with very little deviation from target glucose clamp level, confirming that the glucose-lowering effect of IDeg extends beyond 26 h in Japanese patients with type 1 diabetes. These findings are consistent with the data observed in Caucasian patients, where the duration of action extended beyond 42 h (the duration of euglycemic clamp) at all dose levels (0.4, 0.6 and 0.8 U/kg) in most patients investigated[5].

Several limitations must be considered due to the experimental design of the present study. In particular, the clinical environment is considerably different from the conditions of the glucose clamp procedure. Furthermore, the number of hypoglycemic events observed in the study is likely to be affected by study design, as patients received a fixed dose (0.4 U/kg) of insulin, independent of the individual patient's insulin requirements. It should be noted that, under clinical conditions, IDeg should always be titrated according to individual requirements.

The ultra-long pharmacokinetic and pharmacodynamic properties of IDeg could reduce the impact of missed insulin doses. In a 26-week clinical trial in patients with type 2 diabetes, intervals of 8–40 h were applied between IDeg doses without compromising glucose control or safety in comparison with IGlar administered once daily at the same time each day[20]. Considering that the present study shows that the pharmacokinetic and pharmacodynamic properties of IDeg are preserved in Japanese patients, the ultra-long duration of action and the flat, consistent glucose-lowering effect of IDeg could also reduce the impact of missed or mistimed doses on the efficacy and safety of IDeg in the Japanese population.

As discussed earlier, IDeg has an evenly distributed glucose-lowering effect, is associated with fourfold lower day-to-day variability[7] and significantly reduced rates of nocturnal hypoglycemia compared with IGlar in type 1 diabetes with similar levels of glycemic control[9]. These findings are further supported by a separate 26-week treat-to-target study in Asian patients with type 2 diabetes, including Japanese patients, that reported a lower overall rate of hypoglycemia during the maintenance treatment period with IDeg compared with IGlar[21].

In conclusion, IDeg has a flat and consistent glucose-lowering effect that is evenly distributed across a 24-h dosing interval in Japanese patients. IDeg has an ultra-long duration of action in Japanese patients consistent with that reported in previous studies with Caucasian patients, allowing for once-daily dosing. The same clinical benefits of IDeg, such as flexible dosing, low rates of hypoglycemia and maintenance of glycemic control (including in the event of a missed dose), are therefore expected in this population.

ACKNOWLEDGMENTS

This study was funded by Novo Nordisk. Editorial assistance was provided by ApotheCom ScopeMedical Ltd.

DISCLOSURE

II has no conflicts of interest to declare. KK is a member of advisory panels for Novo Nordisk, Sanwa Kagaku Kogyo, Takeda and Taisho Pharmaceutical Co., Ltd; has received scholarship grants from Chugai, Daiichi Sankyo, MSD, Novo Nordisk and Takeda; and has received speaker honoraria from MSD, Kowa, Sumitomo Dainippon Pharma, Novartis, Novo Nordisk, Takeda and Mitsubishi Tanabe Pharma. KH has received speaker honoraria from Novo Nordisk and Sanofi. LB and HH are employees and shareholders of Novo Nordisk.

REFERENCES

1. Monami M, Marchionni N, Mannucci E. Long-acting insulin analogues vs. NPH human insulin in type 1 diabetes. A meta-analysis. *Diabetes Obes Metab* 2009; 11: 372–378.
2. Szypowska A, Golicki D, Groele L, *et al.* Long-acting insulin analogue detemir compared with NPH insulin in type 1 diabetes: a systematic review and meta-analysis. *Pol Arch Med Wewn* 2011; 121: 237–246.
3. Devries JH, Nattrass M, Pieber TR. Refining basal insulin therapy: what have we learned in the age of analogues? *Diabetes Metab Res Rev* 2007; 23: 441–454.
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: 648–659.
5. Haahr H, Heise T. A review of the pharmacological properties of insulin degludec and their clinical relevance. *Clin Pharmacokinet* 2014; 53: 787–800.
6. 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: 2104–2114.

7. 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: 859–864.
8. Mathieu C, Hollander P, Miranda-Palma B, *et al.* Efficacy and safety of insulin degludec in a flexible dosing regimen vs insulin glargine in patients with type 1 diabetes (BEGIN: Flex T1): a 26-week tandomized, treat-to-target trial with a 26-week extension. *J Clin Endocrinol Metab* 2013; 98: 1154–1162.
9. Ratner RE, Gough SCL, 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: 175–184.
10. Chen M-L. Ethnic or racial differences revisited: impact of dosage regimen and dosage form on pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet* 2006; 45: 957–964.
11. Heise T, Hövelmann U, Nosek L, *et al*. Comparison of the pharmacokinetic and pharmacodynamic profiles of insulin degludec and insulin glargine. *Expert Opin Drug Metab Toxicol* 2015; 11: 1193–1201.
12. 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: 944–950.
13. Kupčová V, Arold G, Roepstorff C, *et al.* Insulin degludec: pharmacokinetic properties in subjects with hepatic impairment. *Clin Drug Investig* 2014; 34: 127–133.
14. Kiss I, Arold G, Roepstorff C, *et al.* Insulin degludec: pharmacokinetics in patients with renal impairment. *Clin Pharmacokinet* 2014; 53: 175–183.
15. Workgroup on Hypoglycemia, American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. *Diabetes Care* 2005; 28: 1245–1249.
16. Rowland M, Tozer TN. Clinical Pharmacokinetics and Pharmacodynamics: Concepts and Applications, 4th edn. Wolters Klower Health/Lippincott William & Wilkins, Philadelphia, 2011.
17. Coester H-V, Heise T, Nosek L, *et al.* Steady state is reached within two to three days of once-daily administration of ultra-long-acting insulin degludec. *Diabetologia* 2012; 55: S373.
18. Haahr H, Ikushima I, Hirao K, *et al.* Similar pharmacokinetic and pharmacodynamic properties of insulin degludec in Japanese and Caucasian subjects with T1DM. Abstract PCS-16-6. *J Diabetes Investig* 2012; 3: 197.
19. Hompesch M, Morrow L, Watkins E, *et al.* Pharmacokinetic and pharmacodynamic responses of insulin degludec in African American, white, and Hispanic/Latino patients with type 2 diabetes mellitus. *Clin Ther* 2014; 36: 507–515.
20. Meneghini L, Atkin SL, Gough SCL, *et al.* 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: 858–864.
21. Onishi Y, Iwamoto Y, Yoo SJ, *et al.* Insulin degludec compared with insulin glargine in insulin-naïve patients with type 2 diabetes: a 26-week, randomized, controlled, Pan-Asian, treat-to-target trial. *J Diabetes Investig* 2013; 4: 605–612.