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Review

Clinical relevance of pharmacokinetic and pharmacodynamic profiles of insulin degludec (100, 200 U/mL) and insulin glargine (100, 300 U/mL) – a review of evidence and clinical interpretation



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ABSTRACT

Aim. – Second-generation basal insulin analogues (e.g. insulin degludec, insulin glargine 300 U/mL), were designed to further extend the duration of insulin action and reduce within-day and day-to-day variability, and consequently hypoglycaemia risk, versus earlier long-acting basal insulins. This review examines the pharmacokinetic/pharmacodynamic characteristics of insulin degludec (100, 200 U/mL) and insulin glargine (100, 300 U/mL), and their influence on clinical outcomes.

Methods. – Available pharmacokinetic/pharmacodynamic publications comparing insulin degludec and insulin glargine were reviewed.

Results. – Both insulin degludec and insulin glargine 300 U/mL have more prolonged and stable pharmacokinetic/pharmacodynamic profiles than the earlier basal insulin analogue, insulin glargine 100 U/mL. Insulin glargine 300 U/mL (0.4 U/kg, morning) showed a more stable pharmacodynamic profile (20% lower within-day variability [$P = 0.047$]) and more even 24-h distribution (over each 6-h quartile) than insulin degludec 100 U/mL, whereas the suprathreshold 0.6 U/kg dose demonstrated a similar, albeit non-significant, trend. In contrast, a second clamp study indicated lower day-to-day variability in the 24-h glucose-lowering effect (variance ratio 3.70, $P < 0.0001$), and more even dosing over each 6-h quartile, with insulin degludec 200 U/mL versus insulin glargine 300 U/mL (0.4 U/kg, evening). Methodological differences and differences in bioequivalence that may explain these discrepancies are discussed.

Conclusions. – Compared with earlier insulin analogues, second-generation basal insulins have improved pharmacokinetic/pharmacodynamic profiles that translate into clinical benefits, primarily reduced nocturnal-hypoglycaemia risk. Additional head-to-head comparisons of insulin degludec and insulin glargine 300 U/mL at bioequivalent doses, utilising continuous glucose monitoring and/or real-world evidence, are required to elucidate the differences in their pharmacological and clinical profiles.

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Introduction

Since the time basal insulins were first developed, there have been ongoing attempts to produce formulations with more

prolonged and/or flatter pharmacokinetic (PK) and pharmacodynamic (PD) profiles over 24 h that better mimic the low and constant physiological basal insulin secretion seen in the fasting state in healthy subjects [1]. Fluctuations in plasma insulin concentration (INS) during the day (within-day variability) and between days (day-to-day variability) can result in variable plasma glucose control, which may expose individuals to periods of hyper- or hypoglycaemia [2]. Insulins with flatter PK profiles (less pronounced peaks and troughs of insulin exposure) and a lower within-day and day-to-day variability will therefore result in a more consistent metabolic action and reduced risk of hypoglycaemia [3]. In turn, this may give individuals and healthcare professionals the confidence to titrate the insulin dose more

Abbreviations: AUC_{GIR+TSS}, steady-state area under the GIR curve for one dosing period; CGM, continuous glucose monitoring; GIR, glucose infusion rate; GIR-AUC, area under the GIR curve; Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; IDeg, insulin degludec; INS, insulin concentration; INS-C, maximum INS; NPH, neutral protamine hagedorn; PD, pharmacodynamic; PK, pharmacokinetic; PTF, peak-to-trough fluctuation; T1DM, type 1 diabetes; T2DM, type 2 diabetes.

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confidently, which can help achieve glycaemic targets, with a degree of flexibility in the timing of administration.

Variations in insulin bioavailability can be assessed using PK endpoints, [4] which are generally considered to be a more specific measure of “intrinsic” variability of the tested insulin preparation. PD endpoints reflect insulin action that can be influenced by within-day and day-to-day differences in insulin sensitivity of individual subjects in their real life [4,5]. Euglycaemic clamp studies are used to assess both PK and insulin action (PD), the latter by determining the glucose infusion rate (GIR), which gives a quantitative evaluation of the biological effect of injected insulin. With therapeutic doses of basal insulin, the GIR primarily reflects the suppression of hepatic glucose production rather than increase in insulin-mediated glucose uptake, if any [5,6]. The area under the GIR curve (GIR-AUC) therefore provides information on blood glucose-lowering effect over a given time interval.

Insulin glargine 100 U/mL (Gla-100), a first-generation long-acting basal insulin analogue, enables glycaemic control to be achieved with once-daily dosing in most people with diabetes [7,8], with a lower risk of hypoglycaemia compared with earlier basal insulin preparations such as neutral protamine Hagedorn (NPH) insulin [9–12] and Lente insulin [13,14]. However, the more recent second-generation basal insulin analogues, such as insulin glargine 300 U/mL (Gla-300) and insulin degludec (IDeg-100 or -200 U/mL [IDeg-100 or IDeg-200]), when compared with Gla-100, have a flatter profile, more prolonged duration of action over 24 h and reduced variability, thus approaching the goal of a more physiological basal insulin, with a lower risk of hypoglycaemia [15–17]. The aim of this publication is to review the available PK/PD data for IDeg-100 or IDeg-200 and Gla-300 in people with diabetes and assess how these may impact on clinical outcomes, such as the risk of hypoglycaemia and the flexibility of dose administration.

The PK/PD profiles of Gla-300, Gla-100 and IDeg-100 or -200

Gla-300 versus Gla-100

Mechanisms of protraction of insulin glargine (Gla-300 and Gla-100)

Insulin glargine (both Gla-100 and Gla-300) differs from human insulin through the substitution of glycine for asparagine at A21 and the retention of two arginine molecules at position B30 [3,15]. The former change ensures stability of the insulin molecule, while the latter is pivotal to shift the isoelectric point [18]. This latter change makes insulin glargine soluble at acidic pH in the vial or pen cartridge, but following administration it precipitates amorphously at the neutral pH of the subcutaneous tissue, thus delaying absorption of its active metabolite M1 (A21-Gly-human insulin), formed following the rapid removal of the B-chain terminal di-arginine molecules by subcutaneous proteases [18,19]. The maximum plasma concentration of M1 occurs at approximately 12 h post injection, with exposure enduring for 24 h and beyond [19–21]. By concentrating insulin glargine to a third of its volume (from 100 U/mL to 300 U/mL), the surface area of the subcutaneous precipitate is reduced by half [22], thereby slowing its dissolution and consequently its absorption from the subcutaneous tissue, resulting in Gla-300 having a more prolonged and flatter PK/PD profile than Gla-100 [23]. Owing to the longer time Gla-300 remains in the subcutaneous tissue prior to release of dimers and monomers, partial degradation by tissue proteases takes place so that ultimately not all of the injected Gla-300 reaches the circulatory system. In fact, the clinical dose of the less bioavailable Gla-300 is greater than that of Gla-100 [24–27] and ensures PK/PD bioequivalence with Gla-100 while maintaining the flatter and more evenly distributed PK/PD profile [6].

Key studies that assessed PK/PD differences between Gla-300 and Gla-100

Single-dose studies. Shiramoto et al, 2015 conducted a single-dose study of Gla-300 (0.4, 0.6 and 0.9 U/kg [0.9 U/kg only used in the European cohort]) or Gla-100 (0.4 U/kg) in Japanese ($n = 18$) and European ($n = 24$) participants with type 1 diabetes (T1DM) [28]. Exposure and metabolic effects were more prolonged and evenly distributed over 24 h with Gla-300 compared with Gla-100 at the 0.4 U/kg dose, with a delayed onset of measurable metabolic effects with Gla-300 [28], due to the prolongation of dissolution of the subcutaneous depot, an observation provided uniquely from single-dose studies. However, the clinical applicability of single-dose studies is relatively limited, as they do not reflect steady-state conditions following repeated daily injections, as occurs in the real lives of people with diabetes.

Steady-state PK/PD studies. Various euglycaemic clamp studies have assessed the steady-state PK/PD of Gla-300 versus Gla-100 in people with diabetes (Table 1). While these studies have some similarities in their study designs (insulin dose and participant populations), they also have important differences (time of dosing, length of clamp and the use of unsmoothed versus smoothed GIR profiles to calculate variability), which will be explored in more detail in this section. These study design differences may help to explain some of the differing results obtained from these studies.

Becker et al, 2015 performed a randomised, double-blind, crossover study involving 30 individuals with T1DM that compared the PK/PD profiles of fixed doses of Gla-300 and Gla-100 [23]. One cohort ($n = 18$) received 0.4 U/kg of Gla-300 during the first 8-day treatment period followed by 0.4 U/kg Gla-100 in the second 8-day treatment period, or vice versa. A second cohort ($n = 12$) received 0.6 U/kg of Gla-300 or 0.4 U/kg of Gla-100 during the first 8-day treatment period, and crossed over to the alternative treatment during the second 8-day treatment period. Basal insulins were administered once daily in the evening. The dose on Day 8 of each treatment period was followed by a 36-h euglycaemic clamp. The steady-state INS and GIR profiles of Gla-300 were more constant, prolonged and more evenly distributed over the 24-h period when compared with Gla-100 (Fig. 1). Blood glucose control (≤ 5.8 mmol/L [≤ 105 mg/dL]) was maintained for approximately 5 h longer with Gla-300 (median 30 h) versus glargine (both Gla-100 and median 25 h) at the 0.4 U/kg/day dose. This study also showed that identical doses of Gla-300 and Gla-100 result in lower 24-h plasma INS and glucose-lowering activity with Gla-300 versus Gla-100.

In a second study by Becker et al, in 2015, the steady-state variability of Gla-300 (with or without polysorbate-20) was assessed in a population of 50 individuals with T1DM. The study included two 24-h euglycaemic clamps using the BiostatTM device, following 6 consecutive days of once-daily administration of 0.4 U/kg Gla-300 [29]. As there was PK/PD bioequivalence between Gla-300 with and without polysorbate-20, Becker et al reported that this allowed variability to be calculated for the overall population. The within-day variability in insulin action, calculated based on unsmoothed GIR, was low, with a median (interquartile range [IQR]) peak-to-trough ratio (PTR) of 1.8 (1.5–2.1) and a median (IQR) peak-to-trough fluctuation (PTF) of 0.6 (0.4–0.7). PTR is calculated by dividing the maximum insulin concentration by the minimum insulin concentration. PTF is calculated by subtracting the minimum from the maximum insulin concentration and dividing by the average insulin concentration. Day-to-day (within-subject) variability (coefficient of variation [CV]) in insulin exposure was 17.4% for INS-AUC_{0–24} and 33.4% for maximum INS (INS-C_{max}). Median fluctuation in unsmoothed GIR (within-day variability) was 1.0 (IQR 0.8–1.1) mg/kg/min, with a PD variability of 34.9% for GIR-AUC_{0–24}.

More recently Porcellati, Lucidi and colleagues reported results from a randomised, single-blind, two-way crossover euglycaemic

Table 1

Key findings described in euglycaemic clamp studies with Gla-300, Gla-100 and IDeg (100 and 200 U/mL).

Study	Mean prior basal (prandial) insulin dose (U/kg/day)	Gla-300 dose, U/kg/day (timing)	Gla-100 dose, U/kg/day (timing)	IDeg dose, U/kg/day (timing)	Clamp	Main study conclusions
Porcellati et al., 2015 [5] 10 participants with T2DM	0.27 (1.19) morning; 0.30 (0.30) evening	N/A	0.4 (morning [n = 5] or evening [n = 5])	N/A	24-h clamp following 9 days of morning or evening dosing	The 24-h glucose infusion rate area under the curve (GIR-AUC _{0–24 h}) was similar with evening and morning dosing (1058 ± 571 and 995 ± 691 mg/kg [P = 0.503]) GIR-AUC _{0–12h} was lower with evening versus morning dosing (357 ± 244 vs. 593 ± 374 mg/kg [P = 0.004]), whereas GIR-AUC _{12–24h} was lower for morning dosing (700 ± 396 vs. 403 ± 343 mg/kg [P = 0.002])
Becker et al., 2015 [23] 30 participants with T1DM Cohort 1: Mean age 44.9 years, BMI 25.9 kg/m ² , duration of diabetes 26.9 years, HbA _{1c} 7.8% (62 mmol/mol); Cohort 2: Mean age 41.0 years, BMI 24.8 kg/m ² , duration of diabetes 26.5 years, HbA _{1c} 8.0% (64 mmol/mol) Inclusion criteria: males/females (18–65 years), BMI 18–30 kg/m ² , T1DM ≥ 1 years, stable insulin regimen for ≥ 2 months, total daily insulin dose < 1.2 U/kg, HbA _{1c} ≤ 9.0%	Cohort 1: 0.30 (0.29); Cohort 2: 0.35 (0.34)	0.4	0.4 (evening)	N/A	36-h clamp following Day 8 dose	Steady-state INS and GIR profiles for Gla-300 were more constant and prolonged and more evenly distributed over 24 h versus Gla-100 Smaller swing in steady-state INS profile over 24 h of < 1 with Gla-300 (median swing [IQR]: 0.8; [0.6–1.0]) as compared with Gla-100 (median swing [IQR]: 1.8; [1.3–2.3]) at 0.4 U/kg/day Euglycaemia (≤ 5.8 mmol/L or ≤ 105 mg/dL) was maintained for ~ 5 h longer (median 30 h) with Gla-300 versus Gla-100
Heise et al., 2015 [37] 66 participants with T1DM Mean age 36.9 years, BMI 24.9 kg/m ² , duration of diabetes 17.6 years, HbA _{1c} 8.1% (65 mmol/mol) Inclusion criteria: males/females (18–65 years), BMI 18–28 kg/m ² , T1DM ≥ 1 year, multiple daily insulin injections for ≥ 12 months, total daily insulin dose < 1.2 U/kg, daily basal insulin ≥ 0.2 U/kg, HbA _{1c} ≤ 10.0%	Not reported	N/A	0.4, 0.6 or 0.8 (evening)	IDeg-100 at 0.4, 0.6 or 0.8 (evening)	42-h clamp in steady state	Mean 24-h GIR profiles were flatter and more stable for all doses of IDeg-100 versus Gla-100 Individual serum INS fluctuated less around the individual mean levels (relative fluctuation at 0.4, 0.6 and 0.8 U/kg/day) with IDeg (14%, 13% and 14%, respectively) than with Gla-100 (22%, 21% and 24%, respectively) Relative fluctuation in GIR (AUC _{GIR,t,SS} ; at 0.4, 0.6 and 0.8 U/kg/day) was lower for IDeg (0.25, 0.37 and 0.38 mg/kg/min, respectively) than for Gla-100 (0.39, 0.54 and 0.73 mg/kg/min, respectively) at steady state
Heise et al., 2012 [36] 54 participants with T1DM Mean Gla-100/IDeg age 36/40 years, BMI 24.8/24.6 kg/m ² , HbA _{1c} 7.5/7.8% (58.5/61.7 mmol/mol) Inclusion criteria: males/females (18–65 years), BMI 18–28 kg/m ² , T1DM ≥ 1 year, multiple daily insulin injections for ≥ 12 months, total daily insulin dose < 1.2 U/kg, daily basal insulin ≥ 0.2 U/kg, HbA _{1c} ≤ 10.0%	Not reported	N/A	0.4 (evening)	IDeg-100 0.4 (evening)	24-h clamps on Days 6, 9 and 12 of a 12-day treatment period	Relative day-to-day variability in glucose-lowering effect was lower for IDeg-100 than for Gla-100 for total metabolic effect (AUC _{GIR,0–24h,SS}) with a CV of 20% versus 82%, respectively Lower within-subject variability with IDeg versus Gla-100 was consistent over time: AUC _{GIR,0–2h,SS} CVs, 33% and 60%, respectively; AUC _{GIR,10–12h,SS} CVs, 32% and 155%, respectively; and AUC _{GIR,22–24h,SS} CVs, 33% and 115%, respectively The day-to-day variability in the GIR fluctuations around the mean during the 24-h dosing interval at steady state (AUC _{GIR,0–24h,SS}) was significantly lower for IDeg-100 (CV 31%) than for Gla-100 (CV 73%), (P < 0.0001)

Table 1 (Continued)

Study	Mean prior basal (prandial) insulin dose (U/kg/day)	Gla-300 dose, U/kg/day (timing)	Gla-100 dose, U/kg/day (timing)	IDeg dose, U/kg/day (timing)	Clamp	Main study conclusions
Becker et al., 2015 [29] 50 participants with T1DM Mean age 42.1 years, mean BMI 25.4 kg/m ² Inclusion criteria: males/females (18–64 years), T1DM ≥ 1 year, total insulin dose < 1.2 U/kg/day, basal insulin dose ≥ 0.2 U/kg/day	0.35 (prandial dose not reported)	0.4 with and without polysorbate-20 (evening)	N/A	N/A	24-h clamp on Day 6	Gla-300 provides predictable, evenly distributed steady-state 24-h coverage with low fluctuation and high reproducibility in insulin exposure Within-subject variability of Gla-300 (i.e. day-to-day variability) for INS-AUC _{0–24} and GIR-AUC _{0–24} were 17.4% (95% CI: 15–21) and 34.8% (95% CI: 30–42), respectively Diurnal fluctuation in exposure (within-day variability) was low, with a median PTR of 1.8 [IQR 1.5–2.1]; correspondingly, the swing degree of fluctuation [median 0.8; IQR 0.5–1.1] and the peak-to-trough fluctuation [median 0.6; IQR 0.4–0.7] were < 1
Bailey et al., 2017 [49] 48 participants with T1DM Cohort 1: mean age 43.7 years, BMI 25.4 kg/m ² , HbA _{1c} 7.4% (57.4 mmol/mol), diabetes duration 23.0 years; Cohort 2: Mean age 41.0 years, BMI 26.0 kg/m ² , HbA _{1c} 7.2% (57.4 mmol/mol), diabetes duration 23.3 years Inclusion criteria: males/females (18–64 years), T1DM > 1 year, stable insulin regimen with total daily insulin dose < 1.2 U/kg, BMI 18–30 kg/m ² , HbA _{1c} ≤ 9.0 %	Cohort 1: 0.34 (0.33); Cohort 2: 0.30 (0.29)	0.4 (morning) 0.6 (morning)	N/A	IDeg-100 0.4 (morning)	30-h clamp following Day 8 dose	Within-day variability of smoothed GIR (GIR-smFL _{0–24}) was 20% lower with Gla-300 than IDeg-100 (<i>P</i> = 0.047) with the mean (SD) fluctuation of the smoothed GIR (GIRsmFL _{0–24}) being 0.38 (0.17) mg/min/kg with Gla-300 versus 0.46 (0.19) mg/min/kg with IDeg-100 Trend towards GIR-smFL _{0–24} being lower for Gla-300 at the 0.6 U/kg/d dose More stable GIR profile for Gla-300 versus IDeg-100 More evenly distributed insulin exposure over 24 h with Gla-300 versus IDeg-100 Relative 24-h fluctuation in insulin exposure was 40% for Gla-300 and 46% for IDeg-100 at the 0.4 U/kg dose “Four-times less day-to-day PD variability with IDeg-200 versus Gla-300”: relative day-to-day variability (in CV %) was 33% for IDeg and 67% for Gla-300; given as variance ratio: 3.70, 95% CI [2.42–5.67], <i>P</i> < 0.0001) 37% lower relative within-day variability with IDeg-200 versus Gla-300 (post hoc analysis, absolute within-day variability as shown in previous studies [36] not presented here)
Heise et al. 2017 [51] 57 participants with T1DM Mean age 45.1 years, BMI 25.6 kg/m ² , HbA _{1c} 7.3% (56.3 mmol/mol) and diabetes duration 21.9 years Inclusion criteria: Males/females (18–64 years), T1DM ≥ 1 year, stable insulin regimen with total daily insulin < 1.2 U/kg/day and daily basal insulin ≥ 0.2 U/kg, BMI 18.5–29.0 kg/m ² , HbA _{1c} ≤ 9.0%	0.32 (prandial dose not reported)	0.4 (evening)	N/A	IDeg-200 0.4 (evening)	24-h clamps on Days 6, 9 and 12 of a 12-day treatment period	Individualised, clinical doses of Gla-300 and Gla-100 resulted in a similar euglycaemic potential under steady-state conditions However, Gla-300 exhibited a more stable profile, with lower variability and more physiological modulation of endogenous hepatic glucose production compared with Gla-100
Porcellati et al., 2018 [6] 18 participants with T1DM Mean age 40 years, T1DM duration 26 years, BMI 23.4 kg/m ² , HbA _{1c} 7.19% (55 mmol/mol) Inclusion criteria: Males/females aged between 18 and 65 years, with disease duration ≥ 5 years, HbA _{1c} between 6.5% (48 mmol/mol) and 8.5% (69 mmol/mol), and BMI > 20 to ≤ 27 kg/m ²	0.30 (0.29)	0.35 (evening)	0.28 (evening)	N/A	24-h clamps after 3 months of dosing	

AUC: area under the curve; BG: blood glucose; BMI: body mass index; CI: confidence interval; CV: coefficient of variation; GIR: glucose infusion rate; Gla-100: insulin glargine 100 U/mL; Gla-300: insulin glargine 300 U/mL; IDeg: insulin degludec; IDeg-100: insulin degludec 100 U/mL; IDeg-200: insulin degludec 200 U/mL; INS: insulin concentration; IQR: interquartile range; N/A: not applicable; PD: pharmacodynamic; PTR: peak-to-trough ratio; T1DM: type 1 diabetes.

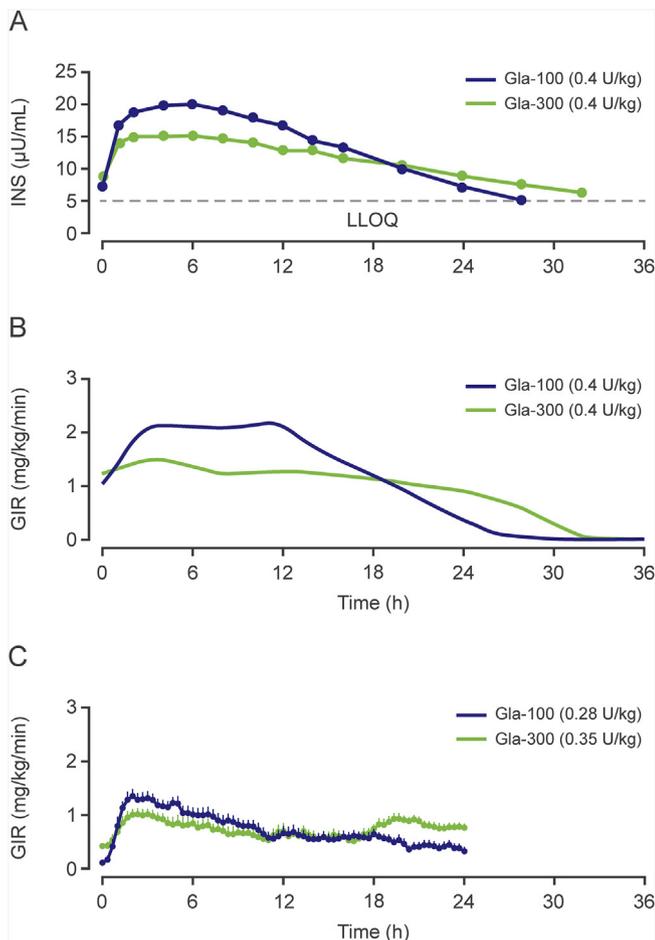


Fig. 1. Steady-state INS profiles (A) and GIR profiles (B) in a euglycaemic clamp study at fixed insulin dose (0.4 U/kg) with Gla-300 and Gla-100 [23], and steady-state INS profiles (C) and GIR profiles in a study using clinical, individual doses of Gla-300 (0.35 ± 0.08 U/kg) and Gla-100 (0.28 ± 0.07 U/kg) [6]. GIR, glucose infusion rate; Gla-100, insulin glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; INS, insulin concentration; LLOQ, lower limit of quantification. Figure 1A and 1B: Reproduced with permission from Becker R.H., et al. New insulin glargine 300 Units.mL⁻¹ provides a more even activity profile and prolonged glycaemic control at steady state compared with insulin glargine 100 Units.mL⁻¹. American Diabetes Association. Diabetes Care, American Diabetes Association, 2015. Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association. Figure 1C: Reproduced with permission from Porcellati F, et al. Pharmacokinetics, Pharmacodynamics, and Modulation of Hepatic Glucose Production With Insulin Glargine U-300 and Glargine U-100 at Steady State With Individualized Clinical Doses in Type 1 Diabetes. Diabetes Care. 2018. doi: 10.2337/dc18-0706. ©2018 by the American Diabetes Association[®]. Diabetes Care 2018 October. Reprinted with permission from the American Diabetes Association[®].

clamp study of Gla-300 versus Gla-100 in people with T1DM (N = 18), using individualised clinical doses of the two insulins [6,30]. The participants, previously receiving Gla-100 as basal insulin, were randomised to either Gla-300 or Gla-100 for 3 months, and then after 2 months of washout were crossed-over to the other basal insulin for a further 3-month period. The basal insulin was titrated to achieve a fasting plasma glucose level of 5.0–6.1 mmol/L (90–110 mg/dL). At the end of each 3-month period a 24-h euglycaemic clamp was performed following evening subcutaneous dosing of the basal insulin under investigation, at the dose used by each individual. The mean (± SD) doses used were 0.35 ± 0.08 U/kg for Gla-300 and 0.28 ± 0.07 U/kg for Gla-100, both maintaining plasma glucose at 5.6 mmol/L (100 mg/dL) for 24 h. Steady-state plasma INS was lower with Gla-300 versus Gla-100 during the first 6-h period (treatment ratio [Gla-300/Gla-100] 0.91 [90% CI: 0.86–0.97]), but was higher for Gla-300 versus

Gla-100 during the last 12-h period (1.38 [90% CI: 1.21–1.56]). Plasma glucose was maintained for 24 h with both Gla-300 and Gla-100 (100.5 ± 1.2 and 101.4 ± 1.8 mg/dL; 0.99 [90% CI: 0.98–1.0]). While the glucose infusion rate was similar with Gla-300 and Gla-100 over the entire 24-h study period (treatment ratio [Gla-300/Gla-100] 1.03 [90% CI: 0.88–1.21]), it was lower with Gla-300 during the first 12 h (0.77 [90% CI: 0.62–0.95]) and higher between 18 and 24 h when compared with Gla-100 (1.91 [90% CI: 1.37–2.68]). Hepatic glucose production was less suppressed on Gla-300 compared with Gla-100 for the initial 6 h, but more suppressed with Gla-300 versus Gla-100 over the last 6 h, suggesting more stable and prolonged insulin action with Gla-300 versus Gla-100 [6]. No between treatment difference in effect on peripheral glucose utilisation was observed. In addition, Gla-300 was more effective than Gla-100 in suppressing lipolysis and ketogenesis for 24 h [30], and glucagon concentration (data on file). It was concluded that despite equivalent glucose efficacy, Gla-300 modulates glucose metabolism more physiologically than Gla-100. The improved PK of Gla-300 was paralleled by improved PD (Fig. 1), explained by less suppression of hepatic glucose output at night and greater suppression in the afternoon versus Gla-100.

Clinical relevance of the PK/PD profiles of Gla-300 and Gla-100. The phase 3 EDITION clinical trial programme evaluated Gla-300 versus Gla-100 in participants with either type 2 diabetes (T2DM) or T1DM [17,24–27,31,32]. These studies demonstrated comparable glycaemic control with Gla-300 and Gla-100, together with a reduced risk of hypoglycaemia with Gla-300, predominantly, but not exclusively, at night and despite a higher Gla-300 dose in T2DM [17,24,26,27,31,32]. In T1DM, hypoglycaemia was similar between Gla-300 and Gla-100 [25], except for nocturnal confirmed (≤ 3.9 mmol/L [≤ 70 mg/dL]) or severe hypoglycaemia in the first 8-weeks of the study (the period during which the largest increase in insulin dose during titration was observed), which was lower with Gla-300 versus Gla-100 (risk ratio 0.69 [95% CI: 0.53–0.91]) [25]. The final dose of Gla-300 required to match the effects of Gla-100 was consistently higher in the EDITION studies [24,26,27,31,32]. The requirement for a higher dose of Gla-300 versus Gla-100 was expected, due to the previously mentioned local degradation of Gla-300 at the injection site and consequently lower bioavailability compared with Gla-100.

These findings have been confirmed in continuous glucose monitoring (CGM) studies. Jinnouchi et al, 2015 conducted a CGM study in 20 Japanese participants with T1DM and demonstrated a slightly lower glucose variability over 24 h, and at night, with Gla-300 versus Gla-100 (administered once daily at bedtime), and a trend towards fewer participants experiencing confirmed or severe hypoglycaemic events with Gla-300 [33]. Bergenstal et al, 2017, reported another CGM study in 59 participants with T1DM showed less variation in the mean 24-h glucose curves with Gla-300 compared with Gla-100 [34]. In this study, the glucose profiles with Gla-300 did not differ between morning and evening injection, whereas with Gla-100 the morning injection was associated with more pronounced peaks and troughs of insulin activity than when Gla-100 was administered in the evening. Finally, this study also showed a significantly lower rate of nocturnal (00:00–05:59 h) confirmed (< 3.0 mmol/L [< 54 mg/dL]) or severe hypoglycaemia with Gla-300 versus Gla-100.

IDeg-100 and IDeg-200 versus Gla-100

Mechanisms of protracted exposure with insulin glargine and IDeg

IDeg, the second-generation acylated insulin after insulin detemir, has a different mode of protraction to glargine (Gla-100 and Gla-300), resulting from the removal of threonine from

position B30, and the addition of a 16-carbon fatty diacid via a glutamic acid spacer at B29. In pharmaceutical formulation in the presence of phenol and zinc, IDeg forms highly stable di-hexamers. After injection, the rapid phenol depletion results in multi-hexamer formation at the injection site. Thereafter, the gradual diffusion of zinc leads to dissociation of the multi-hexamer chains to release monomers, which are absorbed into the systemic circulation. The gradual break-up of the IDeg multi-hexamer chains results in a protracted release of insulin from the subcutaneous depot without precipitation. In the systemic circulation, IDeg binds to albumin before being released into the extracellular space, and circulates in blood largely bound to albumin until it is released for its binding at insulin receptor sites. The two IDeg formulations, Deg-100 and IDeg-200, appear to be bioequivalent [35], but it is possible that there are minor differences in PK/PD characteristics between the two IDeg formulations.

Key studies that define PK/PD differences between IDeg and Gla-100

Two euglycaemic clamp studies comparing IDeg-100 with Gla-100 have been conducted (Table 1) [36,37]. In 2015, Heise et al, demonstrated that the mean 24-h GIR profiles were flatter and more stable for IDeg-100 versus Gla-100, at doses of 0.4, 0.6 or 0.8 U/kg administered once daily in the evening [37]. At steady state, variability in PK (serum insulin levels) and PD (GIR) was lower for IDeg-100 versus Gla-100. However, one should note that, in contrast to glargine, which allows measurement of the free, active insulin in serum, with IDeg the interpretation of PK is limited because it is not possible to measure the “free” active serum IDeg concentration, but only the total concentration (albumin-bound + free fraction). In 2012, Heise et al reported that the day-to-day CV in glucose-lowering effect ($AUC_{GIR,0-24,SS}$; main endpoint) was 20% for IDeg-100 and 82% for Gla-100 at a dose of 0.4 U/kg administered once daily in the evening [36]. However, in addition to the complexity of the experimental procedure, the data of Heise et al, 2012 have not been confirmed by clinical observations and may not be representative of clinical practise. A CGM study by Yamamoto et al, 2016 has reported higher within-day glucose variability for Gla-100 versus IDeg-100 using the measure mean amplitude of glucose excursions (MAGE), which was 144.4 and 121.7 mg/dL for Gla-100 and IDeg-100 over 24 h (1.2 fold difference) [38]. In clinical studies reporting the day-to-day variability in fasting plasma glucose, some have reported no difference [39], whilst another study has reported significantly lower day-to-day variability in fasting plasma glucose with IDeg-100 versus Gla-100 [40]. Higher variability in $AUC-GIR_{total}$ (48% vs. 27%, $P < 0.001$) and GIR_{max} (36% vs. 23%, $P < 0.001$) was reported by Heise et al, 2004, for Gla-100 vs. insulin detemir [41], respectively, a finding again not supported by clinical studies [42,43]. It is not known why variability is so high for Gla-100 in the Heise et al, 2004 study; variability was calculated as the square-root of the within-subject variance using logarithmically transformed end points, whereas other studies calculate variability by dividing the standard deviation of a value by the mean [41]. The authors also speculated that the infusion of human insulin at the start of the glucose clamp potentially affected the variability of Gla-100 more than insulin detemir, as the variability of the GIR data was particularly marked in the first two-hours of the clamp for Gla-100 but not insulin detemir [41], a comment which may imply methodological problems with the experiments. Interestingly, the same investigators, using the same methodology, were not able to confirm their own data, and reported a nearly twice different variability in 24-h glucose lowering for the same dose of Gla-100 in T1DM, i.e. 48% in 2004, but 82% in 2012 [36,41].

Clinical relevance of the PK/PD profiles of IDeg and Gla-100

In clinical studies in people with T2DM, the mean HbA_{1c} reductions were similar for IDeg-100 or IDeg-200 compared with Gla-100, which is unsurprising given the treat-to-target design [39,44], although fasting plasma glucose was consistently lower with IDeg-100 or IDeg-200. In the BEGIN Once Long study in 1030 insulin-naïve people with T2DM, IDeg-100 was associated with lower rates of nocturnal confirmed (< 3.1 mmol/L [< 56 mg/dL]) or severe hypoglycaemia (0.27 vs. 0.46 episodes/patient-year, $P = 0.002$) and anytime severe hypoglycaemia (0.006 vs. 0.021 episodes/patient-year, $P = 0.023$) than Gla-100 [44]. Similar results were seen in the DEVOTE study ($n = 7637$), which showed a significant reduction in severe hypoglycaemia rates with IDeg-100 compared with Gla-100 (3.70 vs. 6.25 episodes/patient-year, $P < 0.001$) [45], and the SWITCH 2 study ($n = 721$), which showed significant reduction in overall symptomatic hypoglycaemia that was confirmed by a blood glucose level < 3.1 mmol/L (< 56 mg/dL) or were severe (219.9 vs. 275.1 episodes/100 patient-year, $P < 0.001$) and at night (72.0 vs. 88.4 episodes/100 patient-year, $P < 0.001$); although no significant differences in severe hypoglycaemia rates were observed in the SWITCH 2 study, this may reflect the smaller participant population in SWITCH 2 versus BEGIN Once Long and DEVOTE [46]. However, in contrast, in the BEGIN Low Volume trial ($n = 460$) comparing Gla-100 with IDeg-200 in insulin-naïve people with T2DM, the rates of overall confirmed hypoglycaemia (defined as events with a blood glucose level of < 3.1 mmol/L [< 56 mg/dL]) or severe hypoglycaemia of 1.42 and 1.22 episodes/patient-year, respectively, and of nocturnal confirmed events (0.28 and 0.18 episodes/patient-year, respectively) were not significantly different between the two basal insulins; this finding may again reflect the smaller participant population in this study versus SWITCH 2 and DEVOTE, and could still be of clinical significance [39]. In addition, FPG reductions were significantly greater with IDeg-200 vs. Gla-100 (23.7 vs. 23.4 mmol/L [-67 vs. -61 mg/dL]) ($P = 0.02$) and insulin dosing was lower (0.53 versus 0.60 U/kg/d) [39].

In the BEGIN Basal-Bolus study in T1DM, Gla-100 and IDeg-100 treatment over a 2-year period were associated with similar reductions in HbA_{1c} (treatment difference -0.04%), not unexpected given the treat-to-target study design, with a lower rate of nocturnal confirmed (< 3.1 mmol/L [< 56 mg/dL]) or severe hypoglycaemia with IDeg-100 compared with Gla-100 (3.9 vs. 5.3 episodes/patient-year, $P = 0.02$) [47]. Similar observations were made over 32-weeks of treatment in the SWITCH 1 study in people with T1DM, with IDeg-100 showing significantly lower rates of confirmed (< 3.1 mmol/L [< 56 mg/dL]) or severe hypoglycaemia overall (2044.6 vs. 2168.4 episodes/100 patient-year, $P = 0.002$) and at night (281.2 vs. 371.9 episodes/100 patient-year, $P < 0.001$) compared with Gla-100, as well as significantly lower rates of severe hypoglycaemia (86.8 vs. 105.2 episodes/100 patient-year, $P = 0.003$) [48].

Gla-300 versus IDeg-100 and IDeg-200

Key studies that define PK/PD differences between Gla-300 and IDeg

Gla-300 was compared directly with IDeg-100 in a euglycaemic clamp study by Bailey et al, 2017, that assessed morning injection of both insulins (Table 1) [49]. This study was performed at Profil (Profil, Neuss, Germany), and consisted of two 8-day treatment periods with participants ($N = 48$) receiving either Gla-300 or IDeg-100 (0.4 U/kg or 0.6 U/kg) once daily before breakfast in the first treatment period, and with the treatment assignment (Gla-300 or IDeg-100) reversed in the second treatment period.

The basal insulin dose on Day 8 of each treatment period (morning dosing) was followed by a 30 h euglycaemic clamp using a ClampArt[®] device (Profil) [49]. The within-day variability of smoothed GIR (GIR-smFL₀₋₂₄) (main endpoint) was significantly lower with Gla-300 than IDeg-100 at the 0.4 U/kg/day dose (treatment ratio Gla-300/IDeg-100: 0.80 [90% CI: 0.66–0.96], $P = 0.047$) (LOESS smoothing factor 0.15), by comparing absolute differences in smoothed individual GIR versus mean individual GIR over 24 h (Fig. 2). For the 0.6 U/kg/day dose the variability of smoothed GIR did not achieve statistical significance (treatment ratio 0.96 [90% CI 0.83 to 1.11]; $P = 0.603$). The reason for this

difference is not known. However, the 0.4 U/kg/day dose is the one clinically relevant for the majority of individuals with T1DM. Total GIR (GIR-AUC₀₋₂₄) was approximately 14% higher with IDeg-100 versus Gla-300 (1947 and 1676 mg/kg, respectively), confirming the expected lower bioavailability of Gla-300 versus IDeg. Over 24 h, Gla-300 exposure was also more evenly distributed in terms of the proportion of GIR-AUC₀₋₂₄ in each 6-h quartile compared with IDeg-100 for both the 0.4 and 0.6 U/kg/day doses (Fig. 2). Gla-300 provided steady-state plateau-like insulin profiles for up to 16 h post dose, followed by a subsequent slow decline (Fig. 2). The insulin-over-time curve for IDeg-100 increased steadily from the time of injection until a maximum concentration at 10 h after dosing, before showing a slow decline (Fig. 2), a profile consistent with that seen in other studies (Fig. 3) [37]. However, as already stated above, PK comparisons of IDeg and Gla-300 are limited, as it is not possible to specifically measure the “free” insulin component of IDeg [37], making the interpretation of PK studies comparing the acylated insulins IDeg and IDet with Gla-100 or Gla-300 problematic [50].

A second clamp study was performed by the same investigators at Profil (Heise et al.) and compared the evening dosing of Gla-300 and IDeg-200 [51]. The study consisted of two 12-day treatment periods with participants ($N = 57$) receiving either Gla-300 or IDeg-200 (0.4 U/kg) once daily at approximately 20:00 h in the first treatment period and treatment assignment (Gla-300 or IDeg-200) being reversed in the second period. GIR and INS were determined over the 24-h euglycaemic clamps on Days 6, 9 and 12 of each treatment period. The methodology of the clamp and the automatic device used was identical to the study described above [49] as both studies were performed at the same site with the same investigators. The steady-state area under the GIR curve for one dosing period ($AUC_{GIR,\tau,SS}$) for Gla-300 was 30% lower than for IDeg-200 (estimated ratio Gla-300/IDeg-200: 0.70 [95% CI: 0.61–0.80], $P < 0.0001$) suggesting differential glucose metabolic effect by the same nominal doses of the two insulins. Under these conditions, a lower day-to-day variability in $AUC_{GIR,\tau,SS}$ (main

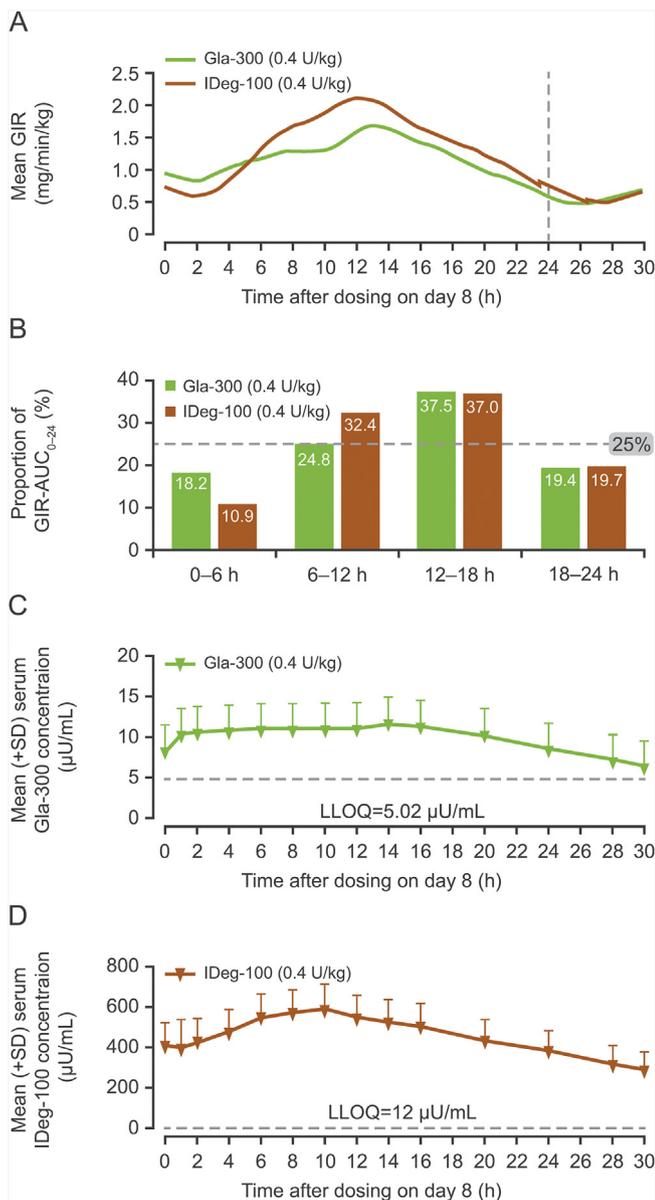


Fig. 2. GIR profiles (A), percentages of 6-h fractions of the total 24-h glucodynamic activity (GIR-AUC₀₋₂₄) (B), and mean serum INS profiles with Gla-300 (C) and IDeg-100 (D) at the 0.4 U/kg/day dose level in steady state [49] AUC, area under the curve; GIR, glucose infusion rate; Gla-300, insulin glargine 300 U/mL; IDeg-100, insulin degludec 100 U/mL; INS, insulin concentration; LLOQ, lower limit of quantification. Reproduced from Bailey TS, Pettus J, Roussel R, Schimder W, Maroccia M, Nassr N, Klein O, Bolli GB, Dahmen R. Morning administration of 0.4 U/kg/day insulin glargine 300 U/mL provides less fluctuating 24-hour pharmacodynamics and more even pharmacokinetic profiles compared with insulin degludec 100 U/mL in type 1 diabetes. *Diabetes Metab* 2018;44(1):15–21. Copyright ©2017 The Authors. Published by Elsevier Masson SAS. <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

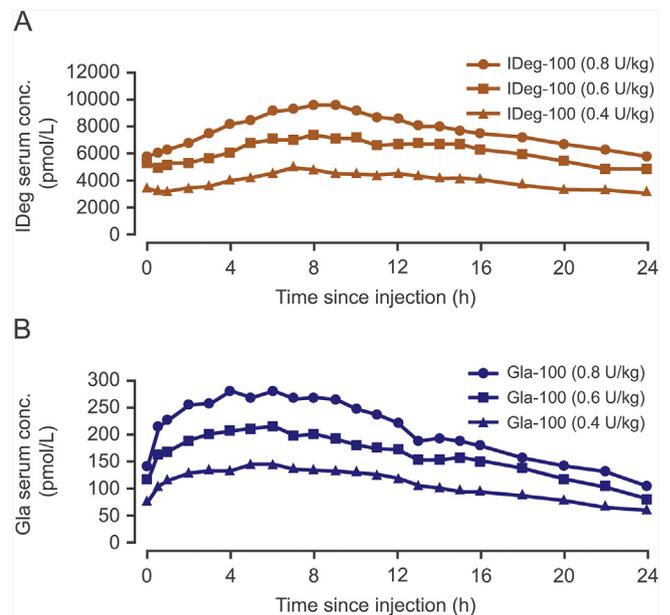


Fig. 3. Steady-state 24-h insulin concentration-time profiles of IDeg-100 (A) and Gla-100 (B) at 3 fixed dose levels in T1DM [37] IDeg, insulin degludec; IDeg-100, insulin degludec 100 U/mL; Gla, insulin glargine; Gla-100, insulin glargine 100 U/mL; T1DM, type 1 diabetes. Reproduced with permission from: Comparison of the pharmacokinetic and pharmacodynamic profiles of insulin degludec and insulin glargine, Heise T, et al., *Expert Opinion on Drug Metabolism & Toxicology*, 2015 Taylor & Francis, reprinted by permission of the publisher Informa UK Limited trading as Taylor & Francis Ltd, <http://www.tandfonline.com>.

endpoint) was reported for IDeg-200 versus Gla-300 at 0.4 U/kg/day: variance ratio Gla-300/IDeg-200: 3.70 (95% CI: 2.42–5.67) (around 4-fold difference with this variability parameter), although the variance values were not reported. The CV for day-to-day variability in glucose-lowering activity was 33% for IDeg-200 and 67% for Gla-300. The distribution of glucose-lowering activity (AUC_{GIR} as a proportion of $AUC_{GIR+TSS}$) across the 6-h quartiles of the 24-h dose period was more consistent for IDeg-200 than Gla-300. In post hoc analyses, in which absolute within-day variability was converted to relative variability to account for the different potency of the study insulins, the relative within-day variability was 37% lower for IDeg-200 than Gla-300 (estimated ratio IDeg-200/Gla-300: 0.63 [95% CI: 0.54–0.73], $P < 0.0001$; absolute values not published).

It is of interest that these two studies, as already said conducted by the same investigators and using an identical euglycaemic clamp technique, provide conflicting findings. The two studies evaluated individuals with T1DM, and their demographic characteristics (age, BMI, duration of diabetes, HbA_{1c} and baseline insulin dose) were similar. In one study IDeg-100 was used [49], while IDeg-200 was used in the other [51]. In the former study, basal insulin was administered in the morning [49], while in the latter it was given in the evening [51]. Above all, the two studies had two different primary aims, i.e., assessing within-day variability in the former [49] and day-to-day variability in the latter [51]. Additionally, in both studies the euglycaemic clamp was not strictly euglycaemic as several subjects had an escape of blood glucose to hyperglycaemic values during the 24 h of the study (Fig. 4). Since

the “variability”, either within-day or day-to-day, is calculated from excursions of GIR above or below a mean value over 24 h, if blood glucose increases above 5.5 mmol/L (100 mg/dL), the algorithm of the machine reduces and eventually stops glucose infusion, creating a fluctuation of GIR that contributes to variability. Thus, a strictly euglycaemic clamp (i.e. a study where blood glucose is < 5.5 mmol/L [100 mg/dL] over the full clamp period) will result in lower variability (both within-day as well as day-to-day) compared with another clamp study where blood glucose increases above 5.5 mmol/L (100 mg/dL) for several hours. As this hyperglycaemia occurred in more participants in the Heise et al study, and with larger glucose excursions in the Gla-300 versus the IDeg-200 group compared with the Bailey et al study (Fig. 4) [49,51], the higher variability of Gla-300 in the Heise et al study is likely to be an artefact owing to failure to maintain euglycaemia in the clamp. This problem was predictable as Heise et al used identical insulin doses for Gla-300 and IDeg-200 and observed lower bioavailability (and therefore lower glucose metabolic effects with the same nominal dose) with Gla-300 versus IDeg-200 [51]. Taken together, these observations suggest that the important question of differences in variability between Gla-300 and IDeg has to be re-assessed by future studies with doses reaching bioequivalent glucose metabolic effects for Gla-300 and IDeg. Finally, if Gla-300 is much more variable than IDeg, then one would expect to see a difference in glucose variability between treatment with Gla-300 versus IDeg (see below BRIGHT study [52]).

The recent comments by Reinhard Becker highlight, in detail, the several flaws and pitfalls of the Heise et al, 2017 study [51,53]. Among other critiques, Becker primarily underlines the fact that the day-to-day pharmacodynamic variability between Gla-300 and IDeg-200 was assessed in the presence of different glucose metabolic effects observed with the two insulins, i.e. there was a different effect of Gla-300 and IDeg-200 on total glucose metabolism ($\sim 30\%$ higher total GIR for IDeg). This implies a different effect of the two insulins on the suppression of hepatic glucose production and stimulation of peripheral glucose utilisation, suggesting that the use of GIR to assess variability under these conditions mixes the different effects of the two insulins in a spurious manner. On the other hand, in their most recent editorial [50], Heise et al reaffirm the validity of their original study, as well as its interpretation [37,50]. As indicated previously, day-to-day and within-day variability should be reassessed in a different experimental model more closely representing the clinical situation, where different basal insulins are compared at different doses needed in individual subjects to match the glucose metabolic effect, as recently demonstrated [6].

Monnier et al, 2018, when considering the discrepancies between the findings of the two studies, questioned whether the euglycaemic clamp test is sufficiently reliable to detect small differences in PD between the insulin preparations [54]. The editorial noted several factors that might explain the reported differences, including the difficulty with the longer-acting analogues of starting the clamp without any residual insulin action from the previous insulin dose, the impact of hepatic glucose production as the insulin concentration falls towards the end of longer clamps of 24 h or longer and the fundamental difficulty in comparing Gla-300 and IDeg owing to the albumin binding properties of IDeg [54].

Finally, it should be noted that in both studies, variability was calculated based on smoothed GIR, which may differ markedly from unsmoothed raw data, as the smoothing algorithms used may have a major impact on the calculated variability [29]. Although the crossover design of these studies may balance out any effects on variability, the impact of such an approach relative to treatment is not known.

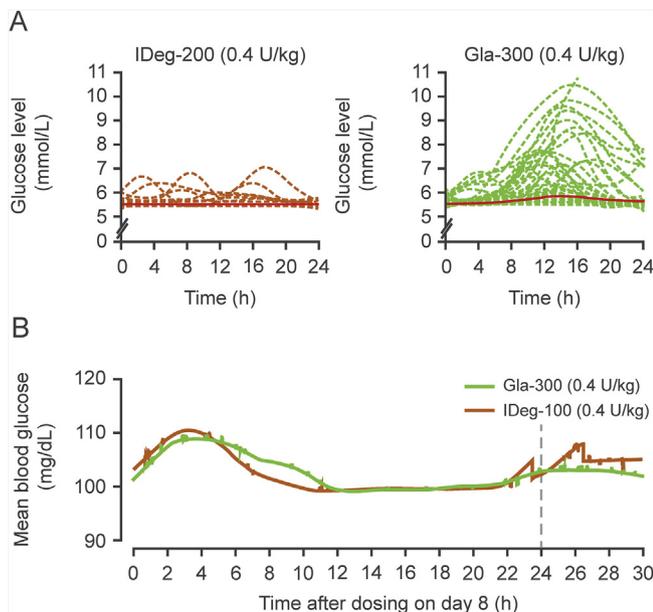


Fig. 4. Glycaemic excursions above the clamp target of 5.5 mmol/L (100 mg/dL) in studies of Gla-300 vs. IDeg: (A) Individual Gla-300 vs. IDeg-200 profiles, Heise et al. 2017 [51] and (B) mean Gla-300 vs IDeg-100 profiles, Bailey et al. 2017 [49] (A) Red dotted line = mean blood glucose in each treatment group. IDeg-100, insulin degludec 100 U/mL; IDeg-200, insulin degludec 200 U/mL; Gla-300, insulin glargine 300 U/mL. A. Reproduced with permission from Heise T., et al. Insulin degludec: Lower day-to-day and within-day variability in pharmacodynamic response compared with insulin glargine 300 U/mL in type 1 diabetes. *Diabetes Obes Metab* 2017;19:1032–9. Copyright©2017 The Authors. *Diabetes, Obesity and Metabolism* published by John Wiley & Sons Ltd. <https://creativecommons.org/licenses/by-nc/4.0/>. B. Reproduced from Bailey TS, Pettus J, Roussel R, Schmider W, Maroccia M, Nassr N, et al. Morning administration of 0.4 U/kg/day insulin glargine 300 U/mL provides less fluctuating 24-hour pharmacodynamics and more even pharmacokinetic profiles compared with insulin degludec 100 U/mL in type 1 diabetes. *Diabetes Metab* 2018;44:15–21. Copyright©2017 The Authors. Published by Elsevier Masson SAS. <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

A recent review by Heise et al [55] analysed pooled data from two PK/PD studies of IDeg versus Gla-100, and also commented on the study of IDeg-200 versus Gla-300 mentioned above [51]. This pooled post hoc analysis of Heise et al [55] indicated lower variability with IDeg-200 versus Gla-300 after participants who achieved blood glucose > 7.0 mmol/L during the clamp were excluded from the calculations. However, the cut-off point of 7.0 mmol/L was arbitrarily elevated as being considered meaningful for such a clamp study, since the algorithm of the clamp machine at Profil would stop GIR and introduce artificial variability for any BG elevation > 5.5 mmol/L. In addition, blood glucose values were not shown, and lack of bioequivalence between identical doses of the two insulins was confirmed. Of note, the consistency of smooth PD (GIR profile) over 24 h with Gla-300 reported in 2015 [23] was not confirmed in this 2017 study, which showed decreased Gla-300 activity at 6–18 h post injection [51]. However, it should also be noted that this Heise et al review did not include the recent study by Bailey et al [49], therefore the full spectrum of available PK/PD evidence is not covered and its conclusions are indeed challenged by the findings of Bailey et al, which demonstrated that the within-day variability was significantly lower with Gla-300 than IDeg-100 at the 0.4 U/kg/day dose [49].

Clinical relevance of the PK/PD profiles of Gla-300 and IDeg

Presently, only one phase 3 clinical trial of Gla-300 versus IDeg has been completed, the BRIGHT study [52]. This head-to-head trial in insulin naïve people with T2DM, uncontrolled on oral anti-hyperglycaemic drugs (with or without, glucagon-like peptide-1 receptor agonists) reported that Gla-300 and IDeg-100 provided similar glycaemic control accompanied by comparable hypoglycaemia during the full 6-month study period and 3–6 month maintenance period, and a lower incidence and rate of anytime (24 h) confirmed (3.9 mmol/L [\leq 70 mg/dL] and 3.0 mmol/L [$<$ 54 mg/dL]) hypoglycaemia with Gla-300 versus IDeg-100 during the initial 3-month titration period [52]. Of note, the BRIGHT study also analysed glucose variability, both as within-day and day-to-day, on Gla-300 and IDeg treatment. Interestingly, no difference between Gla-300 and IDeg has been reported, either in the within-day or day-to-day glucose variability during the 6-month study. Indirectly, these results, obtained with individual clinical, different and bioequivalent doses of the two insulins, are in contrast with the conclusions of Heise et al, 2017, that Gla-300 is 4-times more variable than IDeg [51]. CGM studies and real-life evidence would also greatly assist in identifying the potential clinical impact of subtle PK/PD differences between Gla-300 and IDeg.

Limitations of PK/PD studies

There are known limitations to PK/PD studies utilising euglycaemic clamps to describe the time–action characteristics of insulin preparations, especially those with protraction actions. Between-study comparisons can be especially difficult owing to differences in criteria used to define the onset and end of insulin action. Different plasma concentrations of glucose and insulin at the start of the clamp (i.e. different methodologies in preparing subjects before the euglycaemic clamp), insulin dose used and the degree of insulin sensitivity can also all impact measures of treatment effect. The relevance of clamp studies is further lessened when healthy volunteers or those with T2DM are studied [56], because endogenous insulin secretion is a major confounding factor and buffers the PK/PD differences between basal insulins observed in T1DM. For these various reasons, studies should

preferably be limited to individuals with T1DM; however, performing a euglycaemic clamp in individuals with T1DM is neither easy, nor is there a standardised and generally accepted procedure available. For example, with evening dosing, the subject has had lunch with a subcutaneous injection of rapid-acting insulin analogue, contrasting with morning dosing, which is preceded by an overnight insulin/glucose infusion regimen designed to address the lower insulin sensitivity at night and early morning (dawn phenomenon) [5]. There are also advantages and limitations to automated and manual clamps. Automated clamps make minute-to-minute blood glucose measurement using a glucose sensor, and an algorithm automatically adjusts the GIR [57]. The advantage is that the machine always uses the same algorithm, thereby eliminating the operator bias that may occur with manual clamps, but the problem is that GIR fluctuates artificially every minute because of imprecision of the glucose sensor [57]. Conversely, the manual clamp has the advantage of plasma glucose measurement with a reliable glucose analyser up to every 2.5 minutes and results in a steady GIR over longer intervals compared with the automated clamp. Expertise in manual clamping improves the performance of the clamp, but the skills gained do not transfer to the automated technique, which cannot be regulated by the operator. Interestingly, any head-to-head comparison between automated and manual clamps is currently not possible, as the company that produces and uses the device does not intend to commercialise it [58]. Recently, the importance of careful preparation of subjects prior to a clamp experiment has been emphasised, and the metabolic status over the five hours prior to clamp initiation (T0) has been presented in detail for the first time [6].

PD measurements of variability are confounded by insulin sensitivity, which varies according to time of day [5] and from day-to-day in individuals with and without diabetes, although this represents daily life. In contrast, PK measurements provide a clearer picture of variability in plasma INS following subcutaneous insulin injection, reliant on appropriate assay technology. As within-day glucose variability is a measure linked to the risk of hypoglycaemia seen in clinical practice [2,3] and can be studied using CGM [34], accurate measurement of short-term glycaemic variability is important. Given that PK measures of IDeg do not differentiate between the active free-form and the inactive albumin-bound form in plasma [37], this limits the usefulness of PK measures of variability for IDeg [54].

Conclusions

PK/PD results from euglycaemic clamp studies comparing Gla-300 and Gla-100 concur in demonstrating that Gla-300 has a more stable and prolonged PK/PD profile compared with Gla-100 [23,28]. CGM studies, which provide more clinically relevant insights, also reach similar conclusions [33,34].

The EDITION clinical trial programme confirms that the improved PK/PD profile of Gla-300 versus Gla-100 results in a reduced risk of nocturnal hypoglycaemic events as well as hypoglycaemic events occurring at any time in T2DM, while maintaining comparable glycaemic control [17,24,26,27,31,32]. In T1DM, hypoglycaemia was similar between Gla-300 and Gla-100 [25], except for nocturnal confirmed (\leq 3.9 mmol/L [\leq 70 mg/dL]) or severe hypoglycaemia in the first 8-weeks of the study which was lower with Gla-300 versus Gla-100 (risk ratio 0.69 [95% CI 0.53–0.91])[25]. While the EDITION programme did not demonstrate clear hypoglycaemia benefits in T1DM, a CGM study provided support for the lower glucose variability with Gla-300 ($n = 30$) compared with Gla-100 ($n = 29$), translating into a reduced risk of hypoglycaemia [34], thereby making dose titration safer whilst also allowing more flexibility in injection time. To fully

demonstrate this clinical benefit, other types of studies are required, including observational studies that reflect real-life clinical practice. Future studies should maximise the new knowledge of PK/PD of Gla-300 used at clinical doses, and titrate Gla-300 to prevent nocturnal hypoglycaemia while benefitting from a full 24-h basal insulin distribution.

In T2DM, mean HbA_{1c} reductions achieved with Gla-100, IDeg-100 or IDeg-200 were similar, which is unsurprising given the treat-to target study designs [39,44]. Gla-100, however, was associated with higher rates of nocturnal confirmed (< 3.1 mmol/L [< 56 mg/dL]) or severe hypoglycaemia, and severe hypoglycaemia, versus IDeg-100 [44]. However, this hypoglycaemia benefit with IDeg was not seen in a study comparing Gla-100 and IDeg-200, possibly due to the lower number of participants in this study [39]. Similarly, given the use of a treat-to-target study design, no difference was observed between Gla-100 and IDeg-100 with respect to the lowering of HbA_{1c} in T1DM, although the rate of nocturnal confirmed hypoglycaemia was higher with Gla-100 compared with IDeg-100 [47].

While both Gla-300 and IDeg have more stable and prolonged PK/PD profiles compared with the earlier basal insulin analogue, Gla-100, there have been conflicting results when the PK/PD profiles of the two second-generation basal insulins have been compared directly [49,51]. However, this may reflect differences in study methodologies and analyses. In addition to the inability to compare the pharmacokinetics of Gla-300 and IDeg, as previously discussed, it should also be noted that the euglycaemic clamp technique, when used to compare essentially similar long-acting insulin preparations, cannot be considered sufficiently sensitive to detect small pharmacodynamic differences (especially beyond 20 h post-dosing) because of the well-documented within- and between-day variability in insulin sensitivity. To reach clear conclusions, direct head-to-head comparisons of Gla-300 and IDeg-100 or IDeg-200 in adequately powered PK/PD studies using standardised methodology are required, ensuring that the two insulins reach comparable glucose metabolic effects.

Apart from the BRIGHT study in insulin-naïve people [52], there are currently no data from completed long-term clinical trials directly comparing Gla-300 and IDeg in other T2DM populations such as those on basal or basal-bolus insulin. However, a network meta-analysis suggests that they have comparable clinical benefit [59]. CGM technology would certainly help to confirm whether any PK/PD differences between Gla-300 and IDeg translate into clinically relevant glycaemic benefits. Pragmatic study designs, including observational approaches, may also be required to help elucidate any differences between these insulins in day-to-day clinical practice.

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Author contributions

The authors were involved in the conception of the review article, the generation of the review outline and all subsequent drafts. All authors critically reviewed the manuscript and approved the final version for submission.

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References

- [1] Boll GB, Gottesman IS, Cryer PE, Gerich JE. Glucose counterregulation during prolonged hypoglycemia in normal humans. *Am J Physiol* 1984;247:E206–14.
- [2] Gerich J, Becker RH, Zhu R, Bolli GB. Fluctuation of serum basal insulin levels following single and multiple dosing of insulin glargine. *Diabetes Technol Ther* 2006;8:237–43.
- [3] Shah VN, Moser EG, Blau A, Dhingra M, Garg SK. The future of basal insulin. *Diabetes Technol Ther* 2013;15:727–32.
- [4] Vora J, Heise T. Variability of glucose-lowering effect as a limiting factor in optimizing basal insulin therapy: a review. *Diabetes Obes Metab* 2013;15:701–12.
- [5] Porcellati F, Lucidi P, Cioli P, Candeloro P, Marinelli Andreoli A, Marzotti S, et al. Pharmacokinetics and pharmacodynamics of insulin glargine given in the evening as compared with in the morning in type 2 diabetes. *Diabetes Care* 2015;38:503–12.
- [6] Porcellati F, Lucidi P, Candeloro P, Cioli P, Marinelli Andreoli A, Curti G, et al. Pharmacokinetics, pharmacodynamics, and modulation of hepatic glucose production with insulin glargine U-300 and glargine U-100 at steady state with individualized clinical doses in type 1 diabetes. *Diabetes Care* 2018. <http://dx.doi.org/10.2337/dc18-0706> [Epub ahead of print].
- [7] Swinnen SG, Dain MP, Aronson R, Davies M, Gerstein HC, Pfeiffer AF, et al. A 24-week, randomized, treat-to-target trial comparing initiation of insulin glargine once-daily with insulin detemir twice-daily in patients with type 2 diabetes inadequately controlled on oral glucose-lowering drugs. *Diabetes Care* 2010;33:1176–8.
- [8] Bolli GB, Kerr D, Thomas R, Torlone E, Sola-Gazagnes A, Vitacolonna E, et al. Comparison of a multiple daily insulin injection regimen (basal once-daily glargine plus mealtime lispro) and continuous subcutaneous insulin infusion (lispro) in type 1 diabetes: a randomized open parallel multicenter study. *Diabetes Care* 2009;32:1170–6.
- [9] Bolli GB, Andreoli AM, Lucidi P. Optimizing the replacement of basal insulin in type 1 diabetes mellitus: no longer an elusive goal in the post-NPH era. *Diabetes Technol Ther* 2011;13(1):S43–52.
- [10] Porcellati F, Lin J, Lucidi P, Bolli GB, Fanelli CG. Impact of patient and treatment characteristics on glycemic control and hypoglycemia in patients with type 2 diabetes initiated to insulin glargine or NPH: a post hoc, pooled, patient-level analysis of 6 randomized controlled trials. *Medicine (Baltimore)* 2017;96:e6022.
- [11] Rys P, Wojciechowski P, Rogoz-Sitek A, Nieszczyński G, Lis J, Syta A, et al. Systematic review and meta-analysis of randomized clinical trials comparing efficacy and safety outcomes of insulin glargine with NPH insulin, premixed insulin preparations or with insulin detemir in type 2 diabetes mellitus. *Acta Diabetol* 2015;52:649–62.
- [12] Tricco AC, Ashoor HM, Antony J, Beyene J, Veroniki AA, Isaranuwatthai W, et al. Safety, effectiveness, and cost effectiveness of long acting versus intermediate acting insulin for patients with type 1 diabetes: systematic review and network meta-analysis. *BMJ* 2014;349:g5459.
- [13] Chase HP, Arslanian S, White NH, Tamborlane WV. Insulin glargine versus intermediate-acting insulin as the basal component of multiple daily injection regimens for adolescents with type 1 diabetes mellitus. *J Pediatr* 2008;153:547–53.
- [14] Deiss D, Kordonouri O, Hartmann R, Hopfenmuller W, Lupke K, Danne T. Treatment with insulin glargine reduces asymptomatic hypoglycemia detected by continuous subcutaneous glucose monitoring in children and adolescents with type 1 diabetes. *Pediatr Diabetes* 2007;8:157–62.
- [15] Owens DR. Pharmacokinetics and pharmacodynamics of insulin glargine 300 U/ml in the treatment of diabetes and their clinical relevance. *Expert Opin Drug Metab Toxicol* 2016;12:977–87.
- [16] Ratner RE, Gough SC, Mathieu C, Del Prato S, Bode B, Mersebach H, 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.
- [17] Ritzel R, Rousset R, Bolli GB, Vinet L, Brulle-Wohlhueter C, Glezer S, et al. Patient-level meta-analysis of the EDITION 1, 2 and 3 studies: glycaemic control and hypoglycaemia with new insulin glargine 300 U/ml versus glargine 100 U/ml in people with type 2 diabetes. *Diabetes Obes Metab* 2015;17:859–67.
- [18] Bolli GB, Owens DR. Insulin glargine. *Lancet* 2000;356:443–5.

- [19] Kuerzel GU, Shukla U, Scholtz HE, Pretorius SG, Wessels DH, Venter C, et al. Biotransformation of insulin glargine after subcutaneous injection in healthy subjects. *Curr Med Res Opin* 2003;19:34–40.
- [20] Bolli GB, Hahn AD, Schmidt R, Eisenblatter T, Dahmen R, Heise T, et al. Plasma exposure to insulin glargine and its metabolites M1 and M2 after subcutaneous injection of therapeutic and supratherapeutic doses of glargine in subjects with type 1 diabetes. *Diabetes Care* 2012;35:2626–30.
- [21] Lucidi P, Porcellati F, Candeloro P, Cioli P, Andreoli AM, Marzotti S, et al. Glargine metabolism over 24 h following its subcutaneous injection in patients with type 2 diabetes mellitus: a dose-response study. *Nutr Metab Cardiovasc Dis* 2014;24:709–16.
- [22] Sutton G, Minguet J, Ferrero C, Bramlage P. U300, a novel long-acting insulin formulation. *Expert Opin Biol Ther* 2014;14:1849–60.
- [23] Becker RH, Dahmen R, Bergmann K, Lehmann A, Jax T, Heise T. New insulin glargine 300 Units/mL-1 provides a more even activity profile and prolonged glycemic control at steady state compared with insulin glargine 100 Units/mL-1. *Diabetes Care* 2015;38:637–43.
- [24] Bolli GB, Riddle MC, Bergenstal RM, Ziemien M, Sestakauskas K, Goyeau H, et al. New insulin glargine 300 U/ml compared with glargine 100 U/ml in insulin-naïve people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). *Diabetes Obes Metab* 2015;17:386–94.
- [25] Home PD, Bergenstal RM, Bolli GB, Ziemien M, Rojas M, Espinasse M, et al. New insulin glargine 300 Units/mL versus glargine 100 units/ml in people with type 1 diabetes: a randomized, phase 3a, open-label clinical trial (EDITION 4). *Diabetes Care* 2015;38:2217–25.
- [26] Riddle MC, Bolli GB, Ziemien M, Muehlen-Bartmer I, Bizet F, Home PD, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using basal and mealtime insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 1). *Diabetes Care* 2014;37:2755–62.
- [27] Yki-Jarvinen H, Bergenstal R, Ziemien M, Wardecki M, Muehlen-Bartmer I, Boelle E, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 2). *Diabetes Care* 2014;37:3235–43.
- [28] Shiramoto M, Eto T, Irie S, Fukuzaki A, Teichert L, Tillner J, et al. Single-dose new insulin glargine 300 U/ml provides prolonged, stable glycaemic control in Japanese and European people with type 1 diabetes. *Diabetes Obes Metab* 2015;17:254–60.
- [29] Becker RH, Nowotny I, Teichert L, Bergmann K, Kapitza C. Low within- and between-day variability in exposure to new insulin glargine 300 U/ml. *Diabetes Obes Metab* 2015;17:261–7.
- [30] Lucidi P, Candeloro P, Marinelli Andreoli A, Cioli P, Bolli GB, Fanelli CG, et al. More consistent antilipidic and antiketogenic action of insulin glargine U300 vs. U100 in type 1 diabetes. *Diabetes* 2017;66(Suppl. 1):A270.
- [31] Matsuhisa M, Koyama M, Cheng X, Takahashi Y, Riddle MC, Bolli GB, et al. New insulin glargine 300 U/ml versus glargine 100 U/ml in Japanese adults with type 1 diabetes using basal and mealtime insulin: glucose control and hypoglycaemia in a randomized controlled trial (EDITION JP 1). *Diabetes Obes Metab* 2016;18:375–83.
- [32] Terauchi Y, Koyama M, Cheng X, Takahashi Y, Riddle MC, Bolli GB, et al. New insulin glargine 300 U/ml versus glargine 100 U/ml in Japanese people with type 2 diabetes using basal insulin and oral antihyperglycaemic drugs: glucose control and hypoglycaemia in a randomized controlled trial (EDITION JP 2). *Diabetes Obes Metab* 2016;18:366–74.
- [33] Jinnouchi H, Koyama M, Amano A, Takahashi Y, Yoshida A, Hieshima K, et al. Continuous glucose monitoring during basal-bolus therapy using insulin glargine 300 U mL(-1) and glargine 100 U mL (-1) in Japanese people with type 1 diabetes mellitus: a crossover pilot study. *Diabetes Ther* 2015;6:143–52.
- [34] Bergenstal RM, Bailey TS, Rodbard D, Ziemien M, Guo H, Muehlen-Bartmer I, et al. Comparison of insulin glargine 300 U/mL and 100 U/mL in adults with type 1 diabetes: continuous glucose monitoring profiles and variability using morning or evening injections. *Diabetes Care* 2017;40:554–60.
- [35] Korsatko S, Deller S, Koehler G, Mader JK, Neubauer K, Adrian CL, et al. A comparison of the steady-state pharmacokinetic and pharmacodynamic profiles of 100 and 200 U/mL formulations of ultra-long-acting insulin degludec. *Clin Drug Investig* 2013;33:515–21.
- [36] 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.
- [37] Heise T, Hovelmann U, Nosek L, Hermanski L, Bottcher SG, Haahr H. Comparison of the pharmacokinetic and pharmacodynamic profiles of insulin degludec and insulin glargine. *Expert Opin Drug Metab Toxicol* 2015;11:1193–201.
- [38] Yamamoto C, Miyoshi H, Fujiwara Y, Kameda R, Ichiyama M, Nomoto H, et al. Degludec is superior to glargine in terms of daily glycemic variability in people with type 1 diabetes mellitus. *Endocr J* 2016;63:53–60.
- [39] Gough SC, Bhargava A, Jain R, Mersebach H, Rasmussen S, Bergenstal RM. Low-volume insulin degludec 200 units/ml once daily improves glycemic control similarly to insulin glargine with a low risk of hypoglycemia in insulin-naïve patients with type 2 diabetes: a 26-week, randomized, controlled, multinational, treat-to-target trial: the begin low volume trial. *Diabetes Care* 2013;36:2536–42.
- [40] Aso Y, Suzuki K, Chiba Y, Sato M, Fujita N, Takada Y, et al. Effect of insulin degludec versus insulin glargine on glycemic control and daily fasting blood glucose variability in insulin-naïve Japanese patients with type 2 diabetes: I'D GOT trial. *Diabetes Res Clin Pract* 2017;130:237–43.
- [41] Heise T, Nosek L, Ronn BB, Endahl L, Heinemann L, Kapitza C, 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.
- [42] Renard E, Dubois-Laforgue D, Guerci B, Variability Study G. Non-inferiority of insulin glargine versus insulin detemir on blood glucose variability in type 1 diabetes patients: a multicenter, randomized, crossover study. *Diabetes Technol Ther* 2011;13:1213–8.
- [43] Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Scherthner G. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naïve people with type 2 diabetes. *Diabetologia* 2008;51:408–16.
- [44] Rodbard HW, Cariou B, Zinman B, Handelsman Y, Philis-Tsimikas A, Skjoth TV, et al. Comparison of insulin degludec with insulin glargine in insulin-naïve subjects with Type 2 diabetes: a 2-year randomized, treat-to-target trial. *Diabet Med* 2013;30:1298–304.
- [45] Marso SP, McGuire DK, Zinman B, Poulter NR, Emerson SS, Pieber TR, et al. Efficacy and safety of degludec versus glargine in type 2 diabetes. *N Engl J Med* 2017;377:723–32.
- [46] Wysham C, Bhargava A, Chaykin L, de la Rosa R, Handelsman Y, Troelsen LN, et al. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 2 diabetes: the switch 2 randomized clinical trial. *JAMA* 2017;318:45–56.
- [47] Bode BW, Buse JB, Fisher M, Garg SK, Marre M, Merker L, et al. Insulin degludec improves glycaemic control with lower nocturnal hypoglycaemia risk than insulin glargine in basal-bolus treatment with mealtime insulin aspart in Type 1 diabetes (BEGIN(R)) Basal-Bolus Type 1): 2-year results of a randomized clinical trial. *Diabet Med* 2013;30:1293–7.
- [48] Lane W, Bailey TS, Gerety G, Gumprecht J, Philis-Tsimikas A, Hansen CT, et al. Effect of insulin degludec vs. insulin glargine U100 on hypoglycemia in patients with type 1 diabetes: the SWITCH 1 randomized clinical trial. *JAMA* 2017;318:33–44.
- [49] Bailey TS, Pettus J, Roussel R, Schmider W, Marocchia M, Nassr N, et al. Morning administration of 0.4 U/kg/day insulin glargine 300U/mL provides less fluctuating 24-hour pharmacodynamics and more even pharmacokinetic profiles compared with insulin degludec 100 U/mL in type 1 diabetes. *Diabetes Metab* 2018;44:15–21.
- [50] Heise T, Heckermann S, Hans DeVries J. Variability of insulin degludec and glargine 300 U/mL: A matter of methodology or just marketing? *Diabetes Obes Metab* 2018;20:2051–6.
- [51] Heise T, Norkov M, Nosek L, Kaplan K, Famulla S, Haahr HL. Insulin degludec: lower day-to-day and within-day variability in pharmacodynamic response compared with insulin glargine 300 U/mL in type 1 diabetes. *Diabetes Obes Metab* 2017;19:1032–9.
- [52] Rosenstock J, Cheng A, Ritzel R, Bosnyak Z, Devisme C, Cali AMG, et al. More similarities than differences testing insulin glargine 300 U/mL versus insulin degludec 100 U/mL in insulin-naïve type 2 diabetes: the randomized head-to-head BRIGHT trial. *Diabetes Care* 2018;41:2147–54.
- [53] Becker RHA. In response to: Heise T, Norkov M, Nosek L, Kaplan K, Famulla S and Haahr H. L. (2017) Insulin degludec: Lower day-to-day and within-day variability in pharmacodynamic response compared to insulin glargine U300 in type 1 diabetes. *Diabetes Obes Metab* 2017;19:1032–1039. *Diabetes Obes Metab* 2018;20:2043–7.
- [54] Monnier L, Colette C. Pharmacological variability of insulins degludec and glargine 300 U/mL: equivalent or not? *Diabetes Metab* 2018;44:1–3.
- [55] Heise T, Kaplan K, Haahr HL. Day-to-day and within-day variability in glucose-lowering effect between insulin degludec and insulin glargine (100 U/mL and 300 U/mL): a comparison across studies. *J Diabetes Sci Technol* 2017 [1932296817731422].
- [56] Lucidi P, Porcellati F, Rossetti P, Candeloro P, Cioli P, Marzotti S, et al. Pharmacokinetics and pharmacodynamics of therapeutic doses of basal insulins NPH, glargine, and detemir after 1 week of daily administration at bedtime in type 2 diabetic subjects: a randomized cross-over study. *Diabetes Care* 2011;34:1312–4.
- [57] Heise T, Zijlstra E, Nosek L, Heckermann S, Plum-Morschel L, Forst T. Euglycaemic glucose clamp: what it can and cannot do, and how to do it. *Diabetes Obes Metab* 2016;18:962–72.
- [58] Profil. Profil Germany's range of clinical methods are unrivalled in the industry, <https://www.profil.com/services/methods>; 2017 [accessed 15 June 2017].
- [59] Freemantle N, Chou E, Frois C, Zhuo D, Lehman W, Vlahjanic A, et al. Safety and efficacy of insulin glargine 300 u/mL compared with other basal insulin therapies in patients with type 2 diabetes mellitus: a network meta-analysis. *BMJ Open* 2016;6:e009421.