Effects of insulin degludec and insulin glargine U300 on glycaemic stability in individuals with type 1 diabetes: A multicentre, randomized controlled crossover…

Miura, Hiroshi ; Sakaguchi, Kazuhiko ; Otowa-Suematsu, Natsu ; Yamada, Tomoko ; So, Anna ; Komada, Hisako ; Okada, Yuko ; Hirota, Yushi ;…

(Citation)
Diabetes, Obesity and Metabolism,22(12):2356-2363

(Issue Date)
2020-12

(Resource Type)
journal article

(Version)
Accepted Manuscript

Original Research Papers

Effects of Insulin Degludec and Insulin Glargine U300 on Glycemic Stability in Individuals with Type 1 Diabetes: a Multicenter, Randomized Controlled Crossover Study

Hiroshi Miura,[1] Kazuhiko Sakaguchi,[1,2] Natsu Otowa-Suematsu,[1] Tomoko Yamada,[1] Anna So,[1] Hisako Komada,[1] Yuko Okada,[1] Yushi Hirota,[1] Minoru Kishi,[3] Akihiko Takeda,[4] Qingxiang Chen,[5] Yoichi Tominaga,[5] Tomoaki Nakamura,[6] Yasuo Kuroki,[7] Tomokazu Matsuda,[8] Keiji Iida,[9] Michiko Kajikawa,[10] Takeshi Ohara,[11] Kazuki Yokota,[12] Kenta Hara,[13] Sanshiro Tateya,[14] Yoshikazu Tamori,[1,15] and Wataru Ogawa[1]

[1]Division of Diabetes and Endocrinology and [2]Division of General Internal Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

[3]Department of Internal Medicine, Nishiwaki Municipal Hospital, Nishiwaki, Japan

[4]Department of Diabetic and Metabolic Medicine, Shinko Hospital, Kobe, Japan

[5]Department of Diabetology and Endocrinology, Takatsuki General Hospital, Takatsuki, Japan

[6]Department of Diabetes and Endocrinology, Kobe Rosai Hospital, Kobe, Japan

[7]Department of Internal Medicine, Kobe Century Memorial Hospital, Kobe, Japan

[8]Department of Internal Medicine, Kaisei Diabetes Clinic, Kobe, Japan

[9]Division of Diabetes and Endocrinology, Hyogo Prefectural Kakogawa Medical Center, Kakogawa, Japan

[10]Department of Internal Medicine, Yodogawa Christian Hospital, Osaka, Japan

[11]Department of Diabetes and Endocrinology, Hyogo Brain and Heart Center, Himeji, Japan

[12]Department of Internal Medicine, Yokota Medical Clinic, Akashi, Japan

[13]Department of Diabetes and Endocrine Disease, Kita-harima Medical Center, Ono, Japan

[14]Department of Internal Medicine, Kakogawa Central City Hospital, Kakogawa, Japan

[15]Division of Creative Health Promotion, Department of Social/Community Medicine and Health Science, Kobe University Graduate School of Medicine, Kobe, Japan

Corresponding author: Kazuhiko Sakaguchi, Division of Diabetes and Endocrinology, Department of Internal Medicine, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan. Tel.: +81-78-382-5861. Fax: +81-78-382-2080. Email: kzhkskgc@med.kobe-u.ac.jp

Short running title: IDeg versus IGlarU300 for glycemic stability

Word count (excluding title page, abstract, references, figure legends, and tables): 2950

AIMS

Information on the relative effects of insulin degludec (IDeg) and insulin glargine U300 (IGlarU300) on glycemic stability is limited and inconsistent. We directly compared the effects of these insulins on glycemic stability.

MATERIALS AND METHODS

In this multicenter, crossover trial, 46 individuals with type 1 diabetes and essentially undetectable circulating C-peptide were randomly assigned to the IDeg-first/IGlarU300-second or the IGlarU300-first/IDeg-second groups, and were treated with the respective basal insulins for 4-week periods. Data were collected in the last week of each treatment period. The primary aim was to examine the potential noninferiority of IDeg relative to IGlarU300 with regard to day-to-day variability, as evaluated by the standard deviation (SD), of fasting blood glucose (FBG) levels. Intraday glycemic variability and other parameters were also determined by continuous glucose monitoring (CGM).

RESULTS

The SD of FBG for IDeg was noninferior to that for IGlarU300. The mean of FBG, coefficient of variation (CV) of FBG, and various glycemic variability indexes determined by CGM did not differ between the two insulins. Whereas the administered doses of the insulins also did not differ, the mean glycemic value was lower and the time above (>180 mg/dL) and time below (<70 mg/dL) the target range were shorter and longer, respectively, for IDeg than for IGlarU300.

CONCLUSIONS

Our data suggest that IDeg and IGlarU300 have comparable glucose-stabilizing effects in individuals with type 1 diabetes. However, the glucose-lowering effect of IDeg may be greater than that of IGlarU300 when titrated with a unit-based protocol.

Clinical trial registry number: jRCTs051180138 (Japan Registry of Clinical Trials)

INTRODUCTION

Evidence suggests that, not only hyperglycemia, but also the fluctuation and variability of glycemia are related to the development of complications of diabetes mellitus [1–7]. Increased glycemic variability is associated with a risk of hypoglycemia [8], which also contributes to the development of various health problems related to diabetes mellitus [9,10]. Minimization of glycemic variability is thus an important issue in the choice of treatment for diabetes mellitus.

Insulin degludec (IDeg) and insulin glargine U300 (IGlarU300) are recently introduced ultra–long-acting insulin formulations. The temporal patterns for the glucose-lowering effects of these two insulin analogs have been shown to be flatter than that of IGlarU100 [11,12]. Moreover, treatment with IDeg or IGlarU300 is associated with not only lower intraday [13,14] but also lower interday [15,16] glycemic variability compared with treatment with IGlarU100, suggesting that these new insulin formulations provide a more consistent pharmacological effect for each administration. IDeg and IGlarU300 thus appear to be superior to IGlarU100 with regard to stabilization of glycemia. The lower frequency of hypoglycemia observed with IDeg [17,18] or IGlarU300 [19,20] compared with IGlarU100 might be attributable to these pharmacological properties of the new insulin formulations.

Limited information has been available with regard to direct comparison of the pharmacological properties of IDeg and IGlarU300—in particular, as relates to their effects on glycemic stability. Glucose clamp analyses in one study revealed IDeg to have a flatter diurnal glucose-lowering effect compared with IGlarU300 in individuals with type 1 diabetes [21], whereas a subsequent study showed the opposite result [22]. For individuals with type 2 diabetes, one study revealed no difference in indexes of glycemic variability as assessed by continuous glucose monitoring (CGM) between treatment with IDeg and that with IGlarU300 [23], whereas another study demonstrated better values of some such indexes for treatment with IGlarU300 [24]. No study to date has compared the glycemia-stabilizing properties of these two insulin formulations, either by CGM or by measurement of blood glucose levels, in subjects with type 1 diabetes, whose glycemic variability likely depends largely on the administered insulin formulation because of the lack of the endogenous hormone.

We have now conducted a study to compare directly the effects of IDeg and IGlarU300 on glycemic stability in subjects with type 1 diabetes. We here provide evidence that these two insulin formulations possess similar properties in terms of the stabilization of glycemia.

MATERIALS AND METHODS

Study Design

This multicenter, randomized, crossover, open-label study was conducted in accordance with the Declaration of Helsinki, was registered in the Japan Registry of Clinical Trials (jRCTs051180138), and was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000029630). All participants provided written informed consent before entry into the study. The participating centers and principal investigators of the trial are listed in Supplemental Material.

The study protocol was described previously [25]. In brief, participants had to satisfy all the inclusion criteria and not to meet any exclusion criteria described in Supplemental Table S1. The study recruited 46 outpatients with type 1 diabetes whose fasting C-peptide levels were essentially zero (confirmed to be <0.2 ng/mL at least twice) at 14 medical centers in Japan. Individuals were randomly assigned to the IDeg-first/IGlarU300-second (DG) group or the IGlarU300-first/IDeg-second (GD) group by a centralized allocation process with the use of a computer-generated table of random digits. Participants in each group were treated with each basal insulin for 4 weeks in the assigned order. The last week of each treatment period constituted the data collection period, during which the subjects were directed to measure their blood glucose level seven times a day (fasting, 2 h after breakfast, before lunch, 2 h after lunch, before dinner, 2 h after dinner, and at bedtime) with the use of a self-monitoring of blood glucose (SMBG) device (OneTouch VerioVue; Johnson & Johnson, New Brunswick, NJ). They were also equipped with a professional CGM device (FreeStyle Libre Pro; Abbott Diabetes Care, Alameda, CA) 1 week before the data collection period. The data for administered insulin doses were obtained from the self-reports of the patients. Baseline clinical characteristics and laboratory data were obtained from medical records. Enrollment and follow-up visits are outlined in Supplemental Fig. S1.

Insulin Titration

Participants were instructed to inject basal insulin at the same time each day during the study. To avoid unexpected hypoglycemia, it was recommended that the injected dose of the new basal insulin be reduced by 10% compared with that of the previous basal insulin at switching of the two formulations. If the fasting blood glucose (FBG) level was ≧130 mg/dL for more than three consecutive days, the subject was instructed to increase the basal insulin dose by 1 U. If the FBG level was <70 mg/dL for at least 1 day, the participant was instructed to reduce the basal insulin dose by 2 U. Attending physicians were available to advise patients on basal insulin dose. No change in the type of bolus

insulin formulation was allowed during the trial, although the dose of bolus insulin could be adjusted by the participants.

Study Outcome

The primary aim of the study was evaluation of the noninferiority of IDeg relative to IGlarU300 in terms of day-to-day variability of FBG levels as evaluated by the standard deviation (SD) determined from SMBG data. Secondary end points were (i) the coefficient of variation (CV) for day-to-day variability of FBG levels determined from SMBG data, (ii) intraday glycemic variability calculated from both SMBG and CGM data, (iii) frequency of hypoglycemic events, (iv) duration of hypoglycemia as determined by CGM, and (v) administered basal and bolus insulin doses during the data collection period for each of the two basal insulin formulations. Mean glucose levels and indexes of glycemic variability [SD, CV, M-value, mean amplitude of glycemic excursions (MAGE), and mean of daily difference (MODD)] were calculated from CGM data with the use of EasyGV software (Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK). Time in range (TIR), time above range (TAR), and time below range (TBR) were also calculated from CGM data as the percentages of sensor glucose readings within or outside of the target glucose range [26].

Rationale for Sample Size

As described in detail previously (25), according to a preliminary analysis of day-to-day variability in FBG levels for individuals with type 1 diabetes treated with IDeg, the mean and SD values for the SD of FBG in 30 patients over seven consecutive days were calculated to derive the SD for the intrapatient difference. The noninferiority margin was set as 20 mg/dL. At a significance level of 5% and power of 80%, the sample size was determined as 19 patients per group. Taking into account potential participant dropout and withdrawal during the study period, we set the sample size at 23 patients per group, for a total of 46 patients.

Statistical Analysis

For evaluation of the primary outcome, the difference in interday SD of FBG between the first and second data collection periods was calculated for each participant in both DG and GD groups, and the average was calculated for each group (Dif_{DG} and Dif_{GD}, respectively). By subtracting Dif_{GD} from Dif_{DG} and dividing by 2, the mean difference and 95% CI for the difference between IDeg and IGlarU300 were calculated. The upper limit of the 95% CI had to be less than the noninferiority margin of 20 mg/dL.

The secondary end points were evaluated in the same way. Intergroup differences of normally or nonnormally distributed data were tested for significance with the unpaired Student's *t* test or Mann-Whitney U test, respectively. A *P* value <0.05 was considered statistically significant. All statistical analysis was performed with SPSS software version 22.0 (IBM, Armonk, NY).

RESULTS

A total of 46 randomized participants including 23 individuals in the DG group and 23 in the GD group was enrolled, and all the participants completed the study. The baseline clinical characteristics and laboratory data for the study subjects are shown in Table 1. No participant had missing data for the SD of FBG, the primary end point of the study, with all 46 subjects thus being included in the full analysis set. However, given that 14 participants were excluded from CGM data analysis because of a CGM data coverage ratio of <70%, only the remaining 32 patients were included in the CGM data analysis set (Supplemental Fig. S2). The numbers of participants who injected basal insulin in the morning, at noon, in the evening, and at bedtime were 16, 4, 10, and 16, respectively.

We first examined possible carryover effects for the mean of FBG, SD of FBG, and CV of FBG with repeated-measures ANOVA, but we found no interaction effects between the first and second data collection periods (*P* = 0.07, 0.53, and 0.32, respectively).

The SD of FBG during the IDeg treatment period was noninferior to that during the IGlarU300 treatment period [mean difference of −6.6 mg/dL, with a 95% CI of –16.1 to 3.0 mg/dL (within the noninferiority margin), *P* = 0.17] (Fig. 1A). The mean FBG (mean difference of –6.4 mg/dL, with a 95% CI of –18.4 to 5.7 mg/dL, *P* = 0.29) (Fig. 1B) as well as the CV of FBG (mean difference of –0.1 %, with a 95% CI of –4.6 to 4.3 %, *P* = 0.95) (Fig. 1C) also did not differ between the two treatment periods. The ratio of participants who achieved the target FBG level at the end of treatment did not differ between the two insulins (*n* = 11 [23.9%] for IDeg and *n* = 12 [26.1%] for IGlarU300, *P* = 0.14). The mean of the diurnal blood glucose levels measured with the SMBG device did not differ between the two periods (mean difference of –3.1 mg/dL, with a 95% CI of –10.0 to 3.9 mg/dL, *P* = 0.38). No significant difference in blood glucose levels at each of the seven measurement points during the day was apparent between the two treatment periods (Table 2).

The all-day quartile patterns as well as the median value of the CGM data during the IDeg and IGlarU300 treatment periods are shown in Supplemental Fig. S3. The mean sensor glucose level in CGM analysis of the IDeg treatment period was lower than that

of the IGlarU300 treatment period (mean difference, –9.9 mg/dL, with a 95% CI of –18.4 to –1.4 mg/dL, P = 0.02). Indexes of glucose variability including SD, CV, M-value, MAGE, and MODD did not differ between the two treatment periods (Table 3).

Whereas TIR (70 to 180 mg/dL) did not differ between the two treatment periods, TAR180 (>180 mg/dL) and TBR70 (<70 mg/dL) were significantly shorter and longer, respectively, in the IDeg treatment period than in the IGlarU300 treatment period (TAR180 mean difference of –4.9%, with a 95% CI of –9.1 to –0.6%, P = 0.03; TBR70 mean difference of 4.4%, with a 95% CI of 0.4 to 8.4%, P = 0.04). TAR250 (>250 mg/dL) and TBR54 (<54 mg/dL) did not differ between the two treatment periods, however (Table 4). No severe hypoglycemic events were reported during the study. The frequency of hypoglycemic events (confirmed blood glucose of <70 mg/dL with the use of the SMBG device) did not differ between the two treatment periods (mean difference of 0.1 times per week, with a 95% CI of –0.2 to 0.3 times per week, P = 0.54).

The daily total, basal, and prandial insulin doses did not differ between the IDeg and the IGlarU300 treatment periods (mean difference in total dose of 0.4 U, with a 95% CI of –0.9 to 1.6 U, P = 0.58; mean difference in basal insulin dose of 0.3 U, with a 95% CI of –0.3 to 0.8 U, P = 0.31; mean difference in prandial insulin dose of 0.1 U, with a 95% CI of –1.0 to 1.2 U, P = 0.85).

Six patients reported mild itching and erythema at the CGM wearing site, but these symptoms resolved without treatment. Other notable adverse events were not reported during the study.

DISCUSSION

We have here shown that treatment with IDeg was noninferior to that with IGlarU300 with regard to interday glycemic variability assessed on the basis of the SD of FBG, the primary end point of the study. We also did not detect a significant difference in the CV of FBG or in various parameters related to intra- or interday glycemic variability assessed by CGM, including the SD, CV, M-value, MAGE, and MODD. Our results thus suggest that these two insulin formulations provide comparable glucose-stabilizing effects even in C-peptide–negative individuals with type 1 diabetes, in whom glycemic variability likely depends largely on the pharmacological properties of administered insulin.

Whereas the difference in FBG did not achieve statistical significance, the mean glucose value assessed by CGM was lower, and TBR70 and TAR180 were longer and shorter, respectively, in the IDeg period than in the IGlarU300 period. Moreover, both the median value and the interquartile range of CGM glucose values were lower in the IDeg period at most of the time. Given that the doses of insulin did not differ between the

periods, it is possible that IDeg has a more potent glucose-lowering effect than does IGlarU300. A similar greater glucose-lowering effect of IDeg than of IGlarU300 was also suggested in other studies [23,27,28]. Given that biological actions of insulin analogs are not always same as that of human insulin [29], the units of IDeg and IGlarU300 are determined not simply by the physical quantity but by biological potency, which was investigated with relatively small numbers of subjects [30,31]. Such unit determination may render IDeg more potent than IGlarU300 when standardized by unit. We however cannot completely exclude the possibility that the small, none-significant difference of the dose (mean difference of 0.3U) contributed to the difference of glycemic levels between the two treatment periods.

Whereas the frequency of hypoglycemic events (confirmed blood glucose of <70 mg/dL with the use of the SMBG device) did not differ between the two insulin formulations in the present study, hypoglycemic events were previously found to be more frequent for IDeg than for IGlarU300 [23,24]. This increase in the frequency of hypoglycemic events might also be attributable to the more potent pharmacological action of IDeg.

The U.S. Food and Drug Administration guidelines recommend a washout period equivalent to at least five times the elimination half-life ($t_{1/2}$) of the first drug before switching to a second drug in crossover studies of bioequivalence [32]. In the present study, however, we did not include a washout period between the two treatment periods. Instead, we restricted data collection to the final week of each 1-month treatment period, which likely minimized carryover effects of the previously administered formulation, given that the $t_{1/2}$ of IDeg and IGlarU300 was found to be 25 and 19 h, respectively [33,34]. Indeed, we found no interaction effects between the first and second data collection periods with regard to the mean, SD, and CV of FBG.

With regard to limitations of our study, the timing of basal insulin administration differed among participants. However, no bias in this timing was apparent with the chi-square test in either the DG or GD group ($\chi^2 = 1.30$, degrees of freedom = 3, $P = 0.73$), suggesting that the difference in the timing of injection had little effect on the study results. Another limitation is the relatively small proportion of patients who achieved the target FBG level, which likely reflects the short intervention period of the study. The proportion of patients who achieved the target FBG did not differ between the two groups, however. Moreover, CGM data for analysis were available for only ~70% (32/46) of the study participants. Finally, all the participants of this study were nonobese Japanese adults with undetectable circulating C-peptide. It thus remains to be determined whether the present

results are applicable to individuals of other ethnicities and with different body compositions and insulin-secretory capacities.

In conclusion, our data suggest that IDeg and IGlarU300 exert similar glucose-stabilizing effects in individuals with type 1 diabetes. Our data also suggest that IDeg has a more potent glucose-lowering effect when titrated according to a unit-based protocol. Both interday and intraday glycemic variability as well as unrecognized hypoglycemia are thought to be related to the development of various health problems associated with diabetes mellitus [8,9,35]. It remains to be determined whether these two insulin formulations provide similar outcomes in terms of long-term glycemic control as well as of the prevention of diabetes-related health problems.

Acknowledgments. We thank members of the Best Basal Insulin Study-2 study group for recruitment of patients, collection of data, and helpful discussion.

Data availability. The datasets generated during and/or analyzed the current study are not publicly available but this study are available from the corresponding author on reasonable request.

Duality of Interest. This study, including article-processing charges, was funded by Novo Nordisk Pharma Ltd. KS has received research support from Novo Nordisk Pharma Ltd. as well as lecture fees from Novo Nordisk Pharma and Sanofi. YO, YH, YTa, and WO have each received research support and lecture fees from Novo Nordisk Pharma Ltd. and Sanofi. AT, QC, YTo, TN, YK, TM, KI, TO, KH, and ST have each received lecture fees from Novo Nordisk Pharma Ltd. and Sanofi. All other authors declare no potential conflicts of interest.

Funding. This study was funded by Novo Nordisk Pharma Ltd.

Contribution statement. HM, KS, YTa, and WO contributed to the conception and design of the work. HM, KS, AS, MK, AT, QC, YTo, YK, TM, KI, MK, TO, KY, KH, and ST contributed to the participant-recruitment and date-collection. HM, NO-S, TY, and HK contributed to the data-analysis. YO, YH, and TN contributed to the helpful discussion. HM and KS interpreted the analyses and drafted the manuscript. YTa and WO reviewed manuscript.

All authors approved the final manuscript. KS is the guarantor of the work and as such had full access to all the data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

REFERENCES

1. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321(7258):405-412.
2. Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med. 2004;141(6):421-431.
3. Su G, Mi S, Tao H, et al. Association of glycemic variability and the presence and severity of coronary artery disease in patients with type 2 diabetes. Cardiovasc Diabetol. 2011;10:19.
4. Wang X, Zhao X, Dorje T, Yan H, Qian J, Ge J. Glycemic variability predicts cardiovascular complications in acute myocardial infarction patients with type 2 diabetes mellitus. Int J Cardiol. 2014;172(2):498-500.
5. Niskanen L, Virkamaki A, Hansen JB, Saukkonen T. Fasting plasma glucose variability as a marker of nocturnal hypoglycemia in diabetes: evidence from the PREDICTIVE study. Diabetes Res Clin Pract. 2009;86(2):e15-18.
6. Li TC, Yang CP, Tseng ST, et al. Visit-to-Visit Variations in Fasting Plasma Glucose and HbA1c Associated With an Increased Risk of Alzheimer Disease: Taiwan Diabetes Study. Diabetes Care. 2017;40(9):1210-1217.
7. Lin CC, Li CI, Liu CS, et al. Annual fasting plasma glucose variation increases risk of cancer incidence and mortality in patients with type 2 diabetes: the Taichung Diabetes Study. Endocr Relat Cancer. 2012;19(4):473-483.
8. Zinman B, Marso SP, Poulter NR, et al. Day-to-day fasting glycaemic variability in DEVOTE: associations with severe hypoglycaemia and cardiovascular outcomes (DEVOTE 2). Diabetologia. 2018;61(1):48-57.
9. Frier BM. How hypoglycaemia can affect the life of a person with diabetes. Diabetes Metab Res Rev. 2008;24(2):87-92.
10. Zoungas S, Patel A, Chalmers J, et al. Severe hypoglycemia and risks of vascular events and death. N Engl J Med. 2010;363(15):1410-1418.
11. 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(8):1193-1201.
12. Porcellati F, Lucidi P, Candeloro P, et al. Pharmacokinetics, Pharmacodynamics, and Modulation of Hepatic Glucose Production With Insulin Glargine U300 and

Glargine U100 at Steady State With Individualized Clinical Doses in Type 1 Diabetes. Diabetes Care. 2019;42(1):85-92.

13. Onda Y, Nishimura R, Ando K, Takahashi H, Tsujino D, Utsunomiya K. Comparison of glycemic variability in Japanese patients with type 1 diabetes receiving insulin degludec versus insulin glargine using continuous glucose monitoring: A randomized, cross-over, pilot study. Diabetes Res Clin Pract. 2016;120:149-155.
14. Bergenstal RM, Bailey TS, Rodbard D, et al. Comparison of Insulin Glargine 300 Units/mL and 100 Units/mL in Adults With Type 1 Diabetes: Continuous Glucose Monitoring Profiles and Variability Using Morning or Evening Injections. Diabetes Care. 2017;40(4):554-560.
15. Nakamura T, Sakaguchi K, So A, et al. Effects of insulin degludec and insulin glargine on day-to-day fasting plasma glucose variability in individuals with type 1 diabetes: a multicentre, randomised, crossover study. Diabetologia. 2015;58(9):2013-2019.
16. Iuchi H, Sakamoto M, Matsutani D, Suzuki H, Horiuchi R, Utsunomiya K. The Durability of Basal Insulin Affects Day-to-Day Glycemic Variability Assessed by Continuous Glucose Monitoring in Type 2 Diabetes Patients: A Randomized Crossover Trial. Diabetes Technol Ther. 2017;19(8):457-462.
17. Lane W, Bailey TS, Gerety G, 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(1):33-44.
18. Wysham C, Bhargava A, Chaykin L, 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(1):45-56.
19. Gradiser M, Berkovic MC, Bilic-Curcic I. Changes in HbA1c and hypoglycemic episodes in type 1 diabetes patients after switching to insulin glargine U300: Pilot study. Diabetes Res Clin Pract. 2017;129:144-147.
20. Diez-Fernandez A, Cavero-Redondo I, Moreno-Fernandez J, Pozuelo-Carrascosa DP, Garrido-Miguel M, Martinez-Vizcaino V. Effectiveness of insulin glargine U-300 versus insulin glargine U-100 on nocturnal hypoglycemia and glycemic control in type 1 and type 2 diabetes: a systematic review and meta-analysis. Acta Diabetol. 2019;56(3):355-364.
21. Heise T, Norskov 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(7):1032-1039.

22. Bailey TS, Pettus J, Roussel R, 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(1):15-21.
23. Yamabe M, Kuroda M, Hirosawa Y, Kamino H, Ohno H, Yoneda M. Comparison of insulin glargine 300 U/mL and insulin degludec using flash glucose monitoring: A randomized cross-over study. J Diabetes Invest. 2019;10(2):352-357.
24. Kawaguchi Y, Sawa J, Sakuma N, Kumeda Y. Efficacy and safety of insulin glargine 300 U/mL vs insulin degludec in patients with type 2 diabetes: A randomized, open-label, cross-over study using continuous glucose monitoring profiles. J Diabetes Invest. 2019;10(2):343-351.
25. Miura H, Sakaguchi K, Okada Y, et al. Effects of Insulin Degludec and Insulin Glargine U300 on Day-to-Day Fasting Plasma Glucose Variability in Individuals with Type 1 Diabetes: A Multicenter, Randomized, Crossover Study (Kobe Best Basal Insulin Study 2). Diabetes Ther. 2018;9(6):2399-2406.
26. Battelino T, Danne T, Bergenstal RM, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care. 2019;42(8):1593-1603.
27. Tibaldi J, Hadley-Brown M, Liebl A, et al. A comparative effectiveness study of degludec and insulin glargine 300 U/mL in insulin-naive patients with type 2 diabetes. Diabetes Obesity & Metabolism. 2019;21(4):1001-1009.
28. Rosenstock J, Cheng A, Ritzel R, et al. More Similarities Than Differences Testing Insulin Glargine 300 Units/mL Versus Insulin Degludec 100 Units/mL in Insulin-Naive Type 2 Diabetes: The Randomized Head-to-Head BRIGHT Trial. Diabetes Care. 2018;41(10):2147-2154.
29. Kurtzhals P, Schaffer L, Sorensen A, et al. Correlations of receptor binding and metabolic and mitogenic potencies of insulin analogs designed for clinical use. Diabetes. 2000;49(6):999-1005.
30. https://www.ema.europa.eu/en/documents/assessment-report/tresiba-epar-public-assessment-report_en.pdf.
31. https://www.ema.europa.eu/en/documents/scientific-discussion/lantus-epar-scientific-discussion_en.pdf.

32. U.S. Food and Drug Administration. guidance for industry: bioavailability and bioequivalence studies submitted in NDAs or INDs-general considerations. In:2019.
33. Haahr H, Heise T. A review of the pharmacological properties of insulin degludec and their clinical relevance. Clin Pharmacokinet. 2014;53(9):787-800.
34. 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(4):637-643.
35. Otowa-Suematsu N, Sakaguchi K, Komada H, et al. Comparison of the relationship between multiple parameters of glycemic variability and coronary plaque vulnerability assessed by virtual histology-intravascular ultrasound. J Diabetes Investig. 2017;9(3):610-615.

Table 1 Clinical characteristics and laboratory data for the study participants (*n* = 46) at baseline

Age (years)	53.3	±	14.7
Sex (male/female)	14	/	32
Disease duration (years)	19.4	±	11.6
HbA_{1c} (%)	7.6	±	0.7
Body weight (kg)	58.0	±	11.2
BMI (kg/m^2)	22.2	±	3.4
Systolic blood pressure (mmHg)	123.4	±	14.7
Diastolic blood pressure (mmHg)	71.3	±	11.1
Aspartate aminotransferase (IU/L)	22.3	±	12.1
Alanine aminotransferase (IU/L)	18.5	±	12.9
Serum creatinine (mg/dL)	0.7	±	0.2
eGFR (mL min^{-1} 1.73 m^{-2})	77.7	±	20.8
LDL-cholesterol (mg/dL)	108.6	±	23.1
HDL-cholesterol (mg/dL)	75.8	±	17.4
Triglyceride (mg/dL)	90.1	±	44.8
Prestudy basal insulin			
IDeg (*n*)	35		
IGlarU300 (*n*)	9		
IGlarU100 (*n*)	2		
Complications (%)			
Retinopathy	23.9		
Neuropathy	19.6		
Nephropathy	13.0		

Data are means ± SD unless indicated otherwise. HbA_{1c}, glycated hemoglobin; eGFR, estimated glomerular filtration rate.

Table 2 Differences in SMBG metrics (mg/dL) between IDeg and IGlarU300 (*n* = 46)

Time of day	Group	1st period	2nd period	Mean of difference 1st–2nd	Mean of difference IDeg–IGlar U300 (95% CI)	*P* value
Fasting	DG	164.4 ± 48.6	198.2 ± 48.2	–33.8	–6.4 (–18.4 to 5.6)	0.29
	GD	148.8 ± 37.6	169.9 ± 44.7	–21.0		
AB	DG	208.4 ± 49.3	198.6 ± 52.3	3.6	–1.7 (–18.8 to 15.4)	0.84
	GD	173.4 ± 54.8	168.3 ± 44.9	6.9		
BL	DG	158.9 ± 45.7	169.1 ± 43.6	–10.2	–4.1 (–16.4 to 8.2)	0.50
	GD	147.2 ± 33.1	149.1 ± 32.4	–1.9		
AL	DG	192.5 ± 55.0	182.4 ± 51.1	10.9	7.9 (–8.0 to 23.7)	0.32
	GD	169.5 ± 47.8	173.7 ± 33.1	–4.9		
BD	DG	161.3 ± 38.7	176.4 ± 41.7	–15.1	–8.3 (–20.4 to 3.7)	0.17
	GD	164.3 ± 40.5	162.8 ± 48.4	1.5		
AD	DG	181.4 ± 40.9	192.6 ± 50.8	–7.8	1.4 (–14.3 to 17.1)	0.86
	GD	151.3 ± 42.6	161.9 ± 38.8	–10.6		
BT	DG	176.2 ± 56.9	190.7 ± 64.9	–16.9	–6.0 (–15.9 to 4.0)	0.23
	GD	167.8 ± 35.8	172.8 ± 45.4	–5.0		

Data are means ± SD. *P* values are for comparisons between IDeg and IGlarU300. AB, after breakfast; BL, before lunch; AL, after lunch; BD, before dinner; AD, after dinner; BT, bedtime.

Table 3 Mean glycemic level and glycemic variability indexes for CGM (*n* = 32)

Mean or index	Group	1st period	2nd period	Mean of difference 1st–2nd	Mean of difference IDeg–IGlar U300 (95% CI)	*P* value
Mean (mg/dL)	DG	136.0 ± 29.5	153.8 ± 27.4	–17.9	–9.9 (–18.4 to –1.4)	0.02*
	GD	119.1 ± 25.8	117.2 ± 25.3	1.9		
SD (mg/dL)	DG	59.9 ± 16.6	57.7 ± 14.9	2.3	–1.5 (–6.2 to 3.2)	0.52
	GD	52.4 ± 12.3	47.1 ± 7.1	–5.3		
CV (%)	DG	44.7 ± 10.6	37.8 ± 8.8	6.9	0.9 (–3.5 to 5.3)	0.68
	GD	46.1 ± 11.9	41.0 ± 9.4	5.1		
M-value	DG	314.2 ± 161.4	243.9 ± 106.3	70.3	43.0 (–8.7 to 94.8)	0.10
	GD	300.8 ± 192.6	316.7 ± 154.4	–15.8		
MAGE (mg/dL)	DG	121.5 ± 33.4	126.1 ± 39.3	–4.6	–8.2 (–17.9 to 1.5)	0.09
	GD	111.3 ± 32.6	99.4 ± 22.5	11.8		
MODD (mg/dL)	DG	58.0 ± 14.8	58.0 ± 17.1	–0.1	–4.5 (–9.7 to 0.7)	0.09
	GD	53.8 ± 13.8	44.8 ± 8.9	9.0		

Data are means ± SD. Glycemic variability was calculated with the use of EasyGV software. A default of 120 was used for M-value analysis. *P* values are for comparisons between IDeg and IGlarU300. **P* < 0.05.

Table 4 Percentage of sensor glucose readings within, above, or below the target glucose range (*n* = 32)

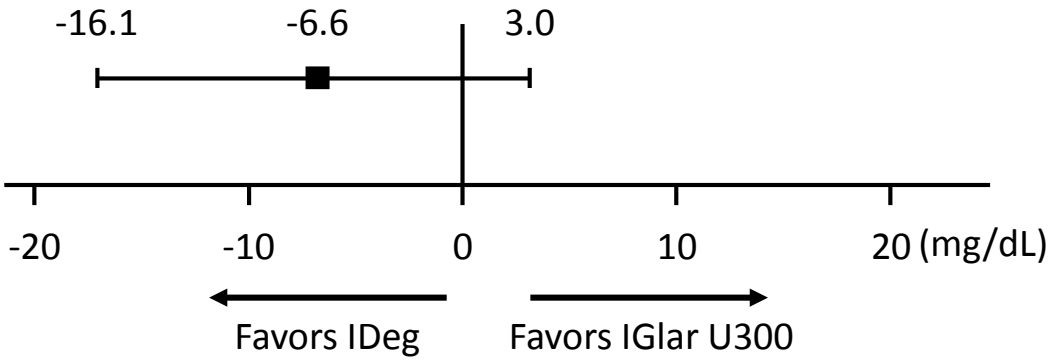
Range (mg/dL)	Group	1st period	2nd period	Mean of difference 1st–2nd	Mean of difference IDeg–IGlar U300 (95% CI)	*P* value
>250	DG	6.5 ± 7.4	8.1 ± 8.0	–1.6	–2.0 (–4.4 to 0.5)	0.11
	GD	3.4 ± 4.3	1.1 ± 1.4	2.3		
>180	DG	22.2 ± 13.6	31.1 ± 16.3	–8.9	–4.9 (–9.1 to –0.6)	0.03*
	GD	15.2 ± 12.7	14.4 ± 11.4	0.8		
70–180	DG	60.8 ± 12.6	60.5 ± 13.1	0.3	0.5 (–3.8 to 4.7)	0.83
	GD	62.6 ± 10.4	63.2 ± 12.3	–0.7		
<70	DG	17.0 ± 13.5	8.4 ± 7.7	8.7	4.4 (0.4 to 8.4)	0.04*
	GD	22.3 ± 13.0	22.4 ± 16.3	–0.1		
<54	DG	8.8 ± 8.2	3.8 ± 4.8	5.0	2.6 (–0.2 to 5.5)	0.07
	GD	11.9 ± 10.1	12.1 ± 11.1	–0.3		

Data are means ± SD. *P* values are for comparisons between IDeg and IGlarU300. **P* < 0.05.

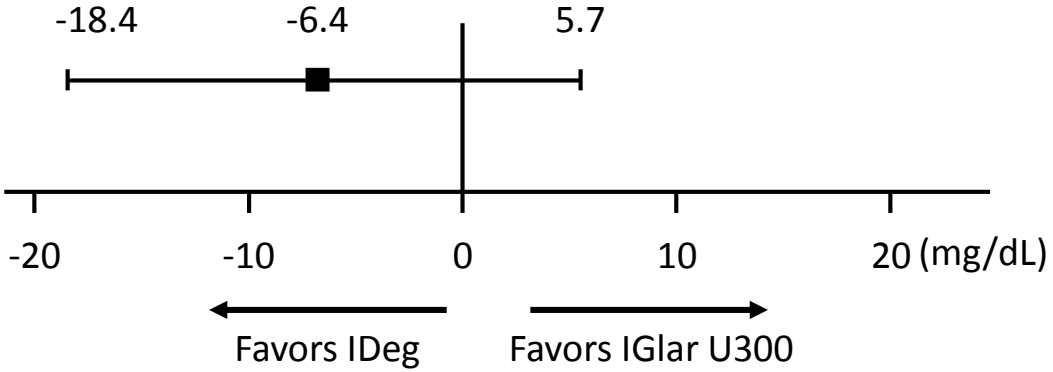
FIGURE LEGEND

Fig. 1 Mean difference and its 95% CI for the SD of FBG (A), mean of FBG (B), and CV of FBG (C) between the IDeg treatment period and the IGlarU300 treatment period (n = 46).

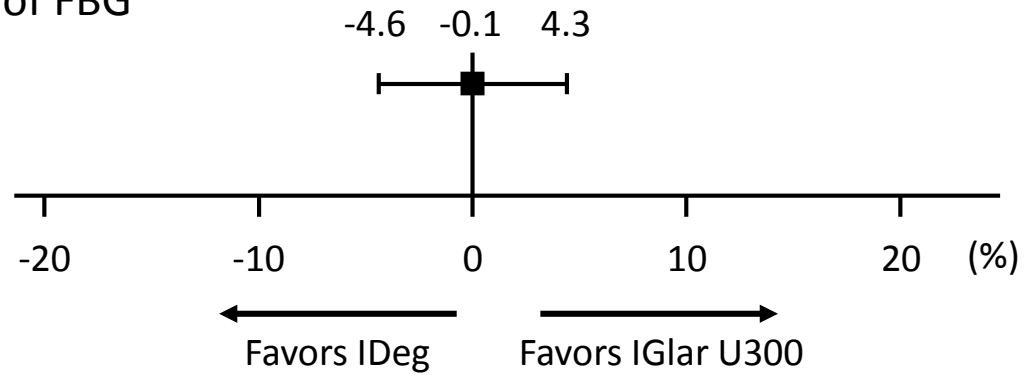
SD of FBG



Mean of FBG



CV of FBG



SUPPLEMENTAL MATERIAL

Effects of Insulin Degludec and Insulin Glargine U300 on Glycemic Stability in Individuals with Type 1 Diabetes: a Multicenter, Randomized Controlled Crossover Study

Participating centers and principal investigators

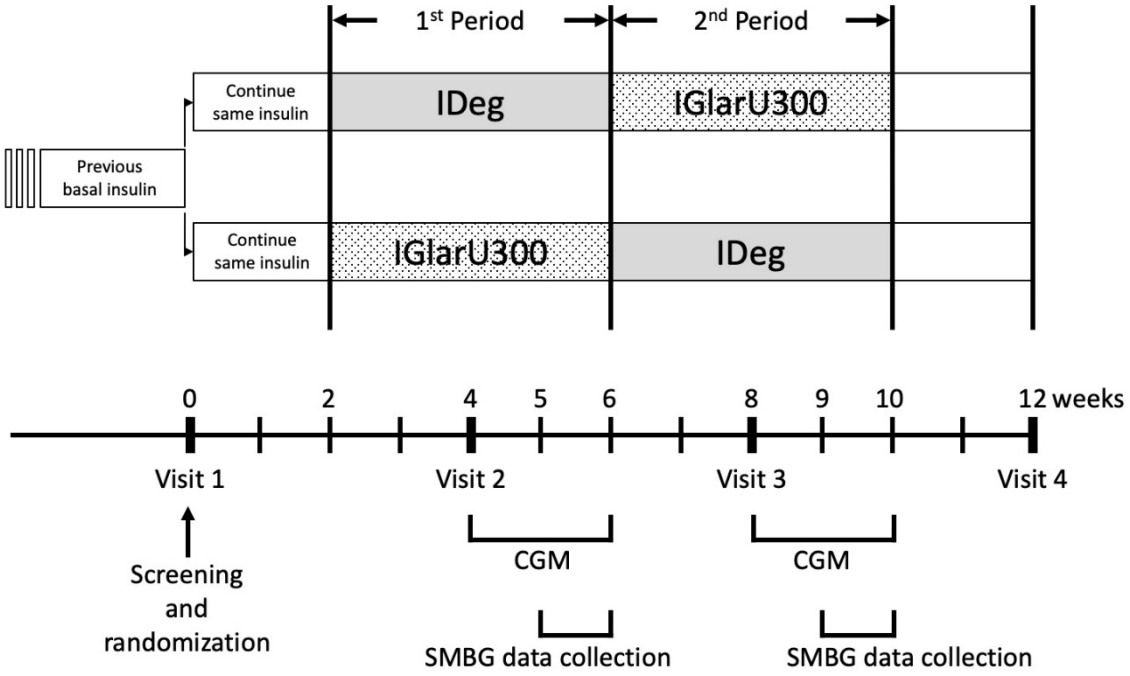
Principal investigators at the participating centers are as follows: KS (Kobe University Hospital, Obara Hospital), MKi (Nishiwaki Municipal Hospital), AT (Shinko Hospital), QC (Takatsuki General Hospital), TN (Kobe Rosai Hospital), YK (Kobe Century Memorial Hospital), TM (Kaisei Diabetes Clinic), KI (Hyogo Prefectural Kakogawa Medical Center), MKa (Yodogawa Christian Hospital), TO (Hyogo Brain and Heart Center), KY (Yokota Medical Clinic), KH (Kita-Harima Medical Center), and ST (Kakogawa Central City Hospital).

Supplemental Table S1 Inclusion and exclusion criteria

Inclusion criteria
[1] Individuals with type 1 diabetes aged ≥20 years with a serum immunoreactive C-peptide level of <0.2 ng/mL (confirmed at least twice).
[2] Individuals who had been treated for at least 1 year with basal-bolus insulin injections.
[3] Individuals with the ability to perform self-monitoring of blood glucose (SMBG).
[4] Individuals with the ability to perform professional continuous glucose monitoring (CGM).

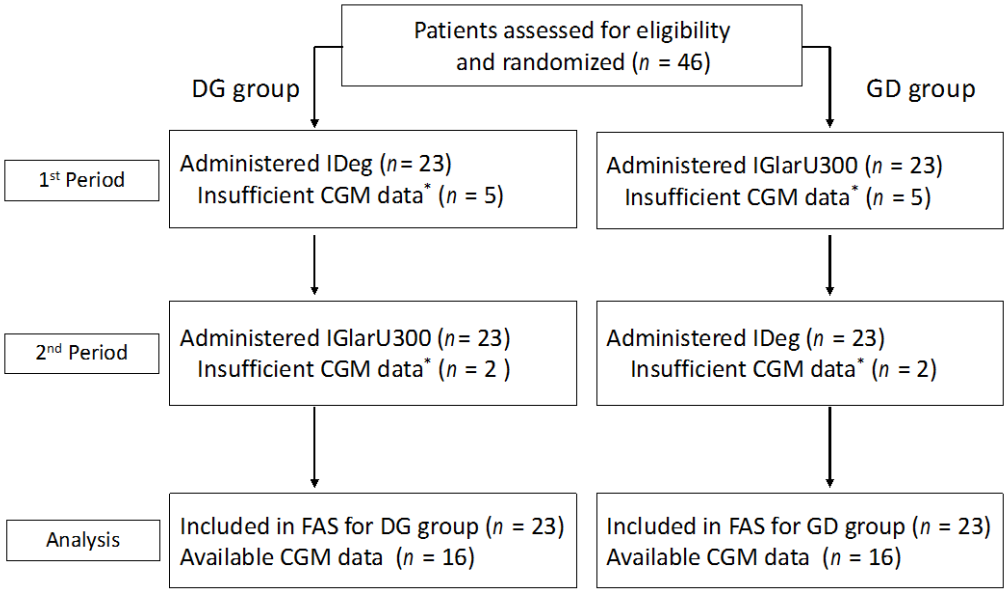
Exclusion criteria
[1] Glycated hemoglobin (HbA_{1c}) level of ≥9.0%.
[2] Treatment with drugs that affect glucose metabolism (such as beta-blockers, corticosteroids, and monoamine oxidase inhibitors).
[3] A history of myocardial infarction, angina, coronary bypass surgery, or heart failure within the previous 6 months.
[4] The presence of severe hypertension (systolic blood pressure of ≥180 mmHg or diastolic blood pressure of ≥100 mmHg).
[5] The presence of severe liver dysfunction (serum aspartate aminotransferase or alanine aminotransferase levels of ≥2.5 times the upper limit of normal).
[6] The presence of severe renal impairment (serum creatinine level of ≥2.0 mg/dL).
[7] Frequently recurring severe hypoglycemia or hospitalization because of severe hypoglycemia or diabetic ketoacidosis within the previous year.
[8] Proliferative diabetic retinopathy with a high risk of hemorrhage.
[9] Actual or possible pregnancy or breastfeeding or no use of adequate contraception (adequate contraceptive measures as recommended by local regulations or practice guidelines).
[10] A diagnosis of cancer.
[11] Diagnosis of a complicating psychiatric disorder.
[12] Alcoholism or other drug addiction.
[13] Diabetes other than type 1, or type 1 diabetes with preserved insulin-secretory capacity.
[14] Rejection of SMBG or CGM.
[15] Declared as otherwise ineligible for the study by an investigator.

Supplemental Fig. S1



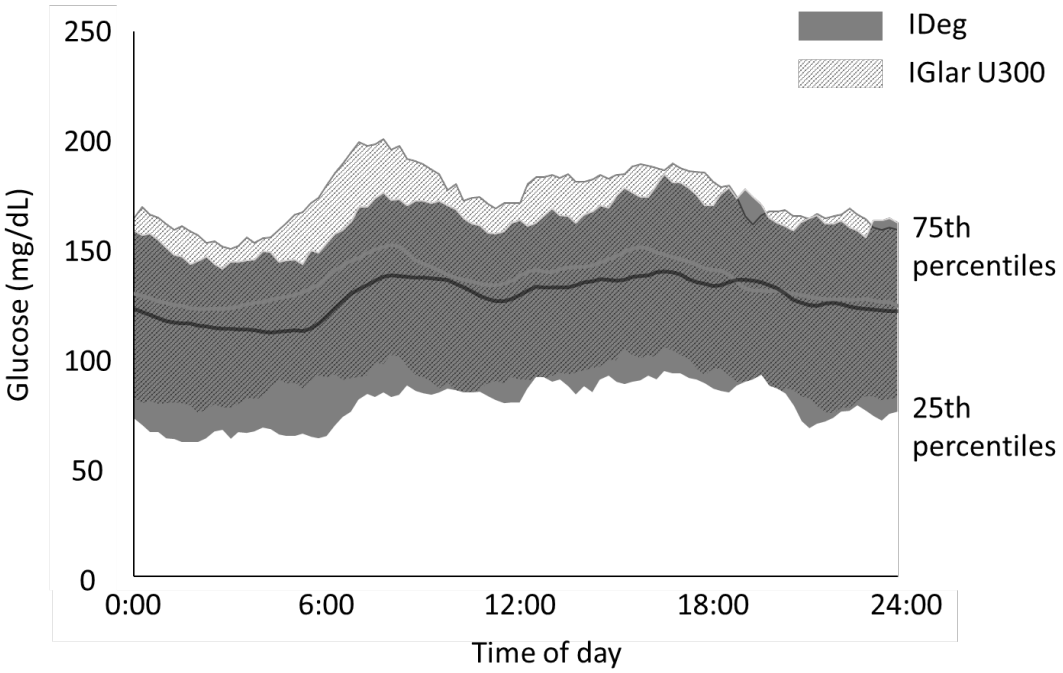
Supplemental Fig. S1 Study design. Eligible patients were randomly allocated to the IDeg-first/IGlarU300-second group (upper arm) or the IGlarU300-first/IDeg-second group (lower arm). In the IDeg-first/IGlarU300-second group, the basal insulin was switched after 4 weeks from IDeg to IGlarU300, whereas in the IGlarU300-first/IDeg-second group the basal insulin was switched after 4 weeks from IGlarU300 to IDeg. Data—including seven SMBG measurements per day, CGM results, and insulin dosage—were collected during the last week of each treatment period.

Supplemental Fig. S2



Supplemental Fig. S2 Consolidating standards of reporting trials (CONSORT) diagram of participants. *These individuals were excluded from the CGM analysis set because of a CGM data coverage ratio of <70%. FAS, full analysis set.

Supplemental Fig. S3



Supplemental Fig. S3 Median and quartile values for sensor glucose levels determined by CGM in each treatment period (n = 32).

The black line (IDeg) and gray line (IGlarU300) denote the median values, and the shaded regions correspond to the interquartile ranges.