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}

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OBJECTIVE

To characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of a new insulin glargine comprising 300 units·mL^{-1} (Gla-300), compared with insulin glargine 100 units·mL^{-1} (Gla-100) at steady state in people with type 1 diabetes.

RESEARCH DESIGN AND METHODS

A randomized, double-blind, crossover study (*N* = 30) was conducted, applying the euglycemic clamp technique over a period of 36 h. In this multiple-dose to steady-state study, participants received once-daily subcutaneous administrations of either 0.4 (cohort 1) or 0.6 units·kg^{-1} (cohort 2) Gla-300 for 8 days in one treatment period and 0.4 units·kg^{-1} Gla-100 for 8 days in the other. Here we focus on the results of a direct comparison between 0.4 units·kg^{-1} of each treatment. PK and PD assessments performed on the last treatment day included serum insulin measurements using a radioimmunoassay and the automated euglycemic glucose clamp technique over 36 h.

RESULTS

At steady state, insulin concentration (INS) and glucose infusion rate (GIR) profiles of Gla-300 were more constant and more evenly distributed over 24 h compared with those of Gla-100 and lasted longer, as supported by the later time (~3 h) to 50% of the area under the serum INS and GIR time curves from time zero to 36 h post dosing. Tight blood glucose control (≤105 mg·dL^{-1}) was maintained for approximately 5 h longer (median of 30 h) with Gla-300 compared with Gla-100.

CONCLUSIONS

Gla-300 provides more even steady-state PK and PD profiles and a longer duration of action than Gla-100, extending blood glucose control well beyond 24 h.

Although insulin analog–based products do not exactly replicate dynamic natural portal insulin release, their insulin concentration (INS) profiles closely mimic those of interprandial endogenous insulin levels. However, meeting glycemic goals with once-daily injections of these agents, while minimizing the frequency of hypoglycemia and

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A slide set summarizing this article is available online.

See accompanying article, p. 541.

widening the flexibility of injection intervals, remains a challenge that new insulin products are being developed to address (1–3).

Insulin glargine mimics the physiology of human insulin, where 31^{B}-Arg-32^{B}-Arg-insulin is a final intermediate of low solubility in the process of endogenous insulin production (4). Substitution of 21^{A}-Asn for Gly results in the molecule insulin glargine (21^{A}-Gly-31^{B}-Arg-32^{B}-Arg-human insulin), which, while chemically stable and fully soluble in acid solution, precipitates amorphously at physiological pH following subcutaneous (SC) injection (5–7), with subsequent slow redissolution. This is different from the retarding principle of other insulins (8–13). In addition, unlike products maintaining solubility after injection, modifications to the concentration of insulin glargine in the injected solution are associated with considerable modifications in the absorption kinetics. It is hypothesized that the size, and hence the surface area, of the SC depot determines redissolution rate. In fact, results of a single-dose euglycemic clamp study in healthy participants, as well as a subsequent single-dose study in people with type 1 diabetes receiving insulin glargine 300 units·mL^{-1} (Gla-300) demonstrated less diurnal variation in glucose-lowering activity than the same dose of glargine 100 units·mL^{-1} (Gla-100) (14,15). Although the former study was inherently limited due to endogenous insulin secretion, these results prompted the clinical development of Gla-300.

This multiple-dose to steady-state study in people with type 1 diabetes enables a more accurate extrapolation of the results to confirmatory clinical trials than the previous single-dose study (14), as the latter only partly captures the effect profile of Gla-300 due to its more gradual onset and extended duration of activity.

The objective of this study was to compare the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of Gla-300 with those of Gla-100 in people with type 1 diabetes under euglycemic clamp conditions, at steady state following once-daily administrations for 8 days (NCT01349855). Serum INS, duration and extent of action, and safety and tolerability profiles were assessed.

RESEARCH DESIGN AND METHODS

Good Clinical Practice

This study was performed in compliance with Good Clinical Practice, the Helsinki Declaration, and local regulations. The protocol was approved by the ethical review board (Ärztekammer Nordrhein) and health authorities (Bundesinstitut für Arzneimittel und Medizinprodukte), and all participants provided written informed consent.

Participants

Males and females aged 18–65 years with a duration of type 1 diabetes ≥1 year on a stable insulin regimen for ≥2 months and receiving a total daily insulin dose of <1.2 units·kg^{-1} were included in this study. Participants were required to have a BMI between 18 and 30 kg·m^{-2}, a fasting serum C-peptide <0.3 nmol·L^{-1}, and glycosylated hemoglobin (HbA_{1c}) ≤9.0% (≤75 mmol·mol^{-1}). Exclusion criteria covered any history or presence of clinically relevant disease (other than diabetes with HbA_{1c} levels ≤9.0% [≤75 mmol·mol^{-1}]).

Study Design and Treatment

This was a single-center, randomized, double-blind, two-treatment, two-period, two-sequence crossover study in two parallel cohorts, evaluating two dose levels of Gla-300, with a standard dose of Gla-100 as an active control, in 30 participants with type 1 diabetes (Supplementary Fig. 1). In cohort 1 (n = 18) participants received, in randomized treatment order, Gla-300 0.4 units·kg^{-1}·day^{-1} in the first treatment period and Gla-100 0.4 units·kg^{-1}·day^{-1} in the second or vice versa. In cohort 2, (n = 12) participants received Gla-300 0.6 units·kg^{-1}·day^{-1} or Gla-100 0.4 units·kg^{-1}·day^{-1}. Each treatment was administered subcutaneously at a periumbilical site, using a 1 mL syringe with 1 unit per 10 μL graduation (Becton, Dickinson and Company, Franklin Lakes, NJ; product number 305502).

The total insulin dose was rounded to the nearest unit, meaning that the integer dose could be accurately administered using the graduation marks for Gla-100. If not exactly divisible by 3, the Gla-300 dose needed to be rounded to the nearest graduation mark (1 unit of Gla-300 corresponding to 10/3 μL). This resulted in either no difference or exactly 1 unit difference between the injected individual Gla-100 and Gla-300 doses, e.g., 27, 28, and 29 units of Gla-100 corresponded to 27, 27, and 30 units of Gla-300.

Study treatments were administered, by medical staff at the study site, once daily at around 8:00 P.M. for 8 days. Gla-300 doses were selected to establish the subtle hyperinsulinemia required for euglycemic blood glucose concentrations in clamp settings, to investigate PK and PD profiles at both a therapeutic and supratherapeutic dose, and to determine the relative effectiveness of doses based on the results of the previous single-dose study (14). As 0.4 units·kg^{-1} is the more clinically relevant dose, this article concentrates on the results of cohort 1, which also allowed comparisons between equal doses of the study treatments. Data on 0.6 units·kg^{-1} Gla-300 (cohort 2) are given as Supplementary Data.

The dose on day 8 of each treatment period was followed by a 36-h euglycemic clamp. An initial in-house period over 3 nights was followed by 4 outpatient days and a final in-house period from the morning of day 8 to end of the clamp. There was a washout period of 5–19 days between consecutive treatment periods.

Participants were to abstain from using other basal or NPH insulins before and during the 8 days of treatment and the 36-h clamp. The last dose of usual basal insulin was to be taken ≥48 h before, and the last dose of NPH insulin was to be taken ≥24 h before, the first injection of Gla-100 or Gla-300. After stopping basal or NPH insulin, other than study administrations of Gla-100 or Gla-300, only short-acting SC insulins were to be used until 12:00 P.M. on day 8; after this time, no SC insulins were to be used.

Participants arrived at the study site in the morning of day 8 after breakfast. Lunch was provided at 12:00 P.M., after which participants were required to fast. All participants were to adjust their own prandial insulin and caloric load, as needed according to blood glucose measurements and closely supported by the treating physician, on days 1–7 and until 12:00 P.M. on day 8.

Assessments

To perform the euglycemic clamp, participants were attached to a Biostator (MTB Medizintechnik, Amstetten, Germany)

~5 h prior to administration of Gla-100 or Gla-300 (~3:00 P.M.). This device determined blood glucose levels in arterialized venous blood (achieved by warming the participant's hand to 60°C) at 1-min intervals and adjusted the glucose infusion in response to changes in blood glucose using a predefined algorithm to achieve and maintain a clamp level of 100 mg·dL^{-1}. Blood glucose was independently measured from venous blood samples at least every 30 min using a laboratory glucose analyzer (Super GL, Hitado, Möhnesee-Delecke, Germany) to ensure accuracy and readjust the Biostator measurements if necessary. Prior to the start of the clamp, the majority of participants had fasting blood glucose levels below 100 mg·dL^{-1} and required glucose infusion to reach the clamp target, in line with the mild hyperinsulinemia caused by the fixed daily doses of treatment given, which were slightly above the usual basal insulin dose. Intravenous infusions of insulin glulisine (infused at a rate of <1 unit·h^{-1} in all cases) were given as necessary by staff at the study site to maintain the clamp level and were stopped shortly prior to study treatment administration. Participants with postdose blood glucose concentration escalating >250 mg·dL^{-1} for 30 min were to receive intravenous insulin (rescue insulin), leading to premature termination.

Clamp-derived PD parameters included the body-weight–standardized glucose infusion rate (GIR), the area under the GIR time curve from time zero to 24 and 36 h postdosing (GIR-AUC$_{0–24/36}$), the time to 50% of GIR-AUC$_{0–24/36}$ ($T_{50\%}$-GIR-AUC$_{0–24/36}$), maximum smoothed GIR (GIR$_{max}$), and time of smoothed blood glucose control within predefined margins (≤105, ≤110, ≤130, and ≤150 mg·dL^{-1} and additionally ≤118 mg·dL^{-1}).

Blood was collected for the determination of INS at hour 0 (predose) on days 1 to 7 and at hour 0 (predose) and 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, 24, 28, 32, and 36 h after dosing on day 8.

A radioimmunoassay with a lower limit of quantification (LLOQ) of 5.02 μU·mL^{-1} was used to determine immunoreactive insulin in serum, i.e., the active metabolites plus the parent compound. Separate glargine metabolite concentrations were determined in plasma with liquid chromatography–tandem mass spectroscopy and reported elsewhere (16). Noncompartmental methods were used to determine the area under the serum INS time curve from time zero to 24 and 36 h post dosing (INS-AUC$_{0–24/36}$), time to 50% of INS-AUC$_{0–24/36}$ ($T_{50\%}$-INS-AUC$_{0–24/36}$), maximum INS (INS-C_{max}), and swing ([C_{maxss} − C_{24ss}]/C_{24ss}).

Statistical Analysis

Statistical analyses were performed separately for each cohort, comparing test (Gla-300) with reference (Gla-100) treatment. Analyses included graphical presentations of PK and PD profiles, lists and descriptive statistics of derived PK and PD parameters by treatment and cohort, and duration of euglycemia and blood glucose control. A linear mixed-effects model on log-transformed data was applied to estimate pairwise treatment ratios for time-independent parameters (e.g., AUCs), while exact Hodges–Lehmann estimators with 90% CI for the median of treatment differences were applied to explore time-related parameters (e.g., $T_{50\%}$-AUCs).

For descriptive statistical analysis, the predose serum INS values on day 8 were set to the concentrations measured 24 h after last dosing. Participants with at least one sample value >LLOQ per treatment were included for PK analysis. Mean values and their associated statistics were generated from unrounded numbers.

GIR-AUC$_{0–24/36}$ was calculated according to the rectangular rule for the stepwise constant function with timescale in minutes. A locally weighted regression in smoothing scatterplots (LOESS; smoothing factor of 0.06) technique was used for the smoothing of GIR, and Biostator measured blood glucose to determine GIR$_{max}$ and time of blood glucose control within predefined margins (≤105, ≤110, ≤118, ≤130, and ≤150 mg·dL^{-1}). LOESS smoothing was also used to visualize GIR profiles.

Safety

Safety evaluations were performed for all participants exposed to any study treatment. Safety assessments included adverse events that were spontaneously reported by the participant or observed by the investigator. Adverse events were assessed for severity and possible relationship to study medication. Hypoglycemic events were assessed according to American Diabetes Association definitions (17).

RESULTS

Participants

In cohort 1, 1 female and 17 males with type 1 diabetes, with a mean age of 44.9 (SD 7.3) years, a mean diabetes duration of 26.9 (10.5) years, a mean BMI of 25.9 (2.1) kg·m^{-2}, mean HbA_{1c} of 7.8 (0.6)% (62 [7] mmol·mol^{-1}), and a mean fasting serum C-peptide of 0.02 (0.03) nmol·L^{-1} were treated. The mean baseline daily basal insulin supplementation was 0.30 (0.06) units·kg^{-1}, and all participants used ≤0.4 units·kg^{-1}. Mean daily prandial insulin supplementation at baseline was 0.29 (0.09) units·kg^{-1}. One participant was withdrawn after treatment period 1 for a non-drug-related adverse event (ventricular extrasystoles). The characteristics of participants in cohort 2 are shown in Supplementary Table 1.

Dosing

For cohort 1, the mean injected doses were 33.78 (SD 4.02) and 33.67 (4.43) units for Gla-100 and Gla-300, respectively, and for cohort 2, they were 30.33 (5.55) and 45.75 (8.40) units, respectively, after accounting for rounding.

Insulin PK

Summaries of steady-state PK parameters of insulin after multiple once-daily doses of Gla-300 and Gla-100 are provided in Table 1 and Supplementary Table 2. Mean serum INS profiles are displayed in Fig. 1. Individual profiles are presented in Supplementary Figs. 2 and 3 in addition to mean profiles displaying measures of dispersion. One participant in cohort 1 had INS values <LLOQ with both treatments despite euglycemia, and a second was withdrawn after period 1 due to a non-drug-related adverse event. One participant in cohort 2 on Gla-100 required rescue insulin after 27 h, and his samples thereafter were set to zero for the corresponding period.

Insulin exposure with Gla-300 was quantifiable in >50% of participants until 32 h after 0.4 units·kg^{-1}·day^{-1}, compared with 28 h after 0.4 units·kg^{-1}·day^{-1} Gla-100 (Fig. 1). $T_{50\%}$-INS-AUC$_{0–36}$ was significantly longer for Gla-300 compared with Gla-100 (Table 1 and Supplementary Table 2). Exposure to Gla-300 was more evenly distributed

Table 1—PK parameters after multiple doses in steady state

	Gla-100 0.4 units·kg^{-1}	Gla-300 0.4 units·kg^{-1}	Treatment ratio T/R (90% CI)	Treatment difference T − R (90% CI)
n	17‡	16‡§		
INS-C_{max}, μU·mL^{-1}*	23.4 ± 8.4	18.1 ± 6.5	0.78 (0.68 to 0.91)	
INS-$AUC_{0–24}$, μU·h·mL^{-1}*	389 ± 141	331 ± 140	0.83 (0.69 to 1.00)	
INS-$AUC_{0–36}$, μU·h·mL^{-1}*	438 ± 167	418 ± 186	0.93 (0.77 to 1.12)	
$T_{50\%}$-INS-$AUC_{0–24}$, h†	9.6 (9–10)	10.4 (10–11)		0.65 (0.06 to 1.25)
$T_{50\%}$-INS-$AUC_{0–36}$, h†	10.9 (10–12)	14.0 (12–15)		2.05 (1.35 to 3.03)
INS-$t_{1/2}$, h*	13.5 ± 6.9	19.0 ± 6.4		—
ΔINS, μU·mL^{-1}†‖	15 (11–18)	9 (5–10)		—
Swing†¶	1.8 (1.3–2.3)	0.8 (0.6–1.0)		—

All data shown from cohort 1; Gla-100 0.4 units·kg^{-1} (reference) versus Gla-300 0.4 units·kg^{-1} (treatment). Data from cohort 2 are reported in Supplementary Table 2. INS-$t_{1/2}$, terminal half-life of serum INS; R, reference; T, treatment. *Mean ± SD. †Median (interquartile range). ‡1 of 18 subjects with INS <LLOQ. §One withdrawal prior to period 2. ‖INS-C_{maxss} − INS-C_{24ss}. ¶(INS-C_{maxss} − INS-C_{24ss})/INS-C_{24ss}.

over the clamp period compared with Gla-100, as supported by the more linear graphical representation of the time to a given percentage of INS-$AUC_{0–36}$ (Fig. 2). The smaller swing in steady-state concentration profile of <1 with Gla-300 0.4 units·kg^{-1} was indicative of a reduced fluctuation in insulin exposure, and this was no different with the higher dose of 0.6 units·kg^{-1}. The results confirm that, at steady state, Gla-300 confers more constant and prolonged PK profiles compared with Gla-100.

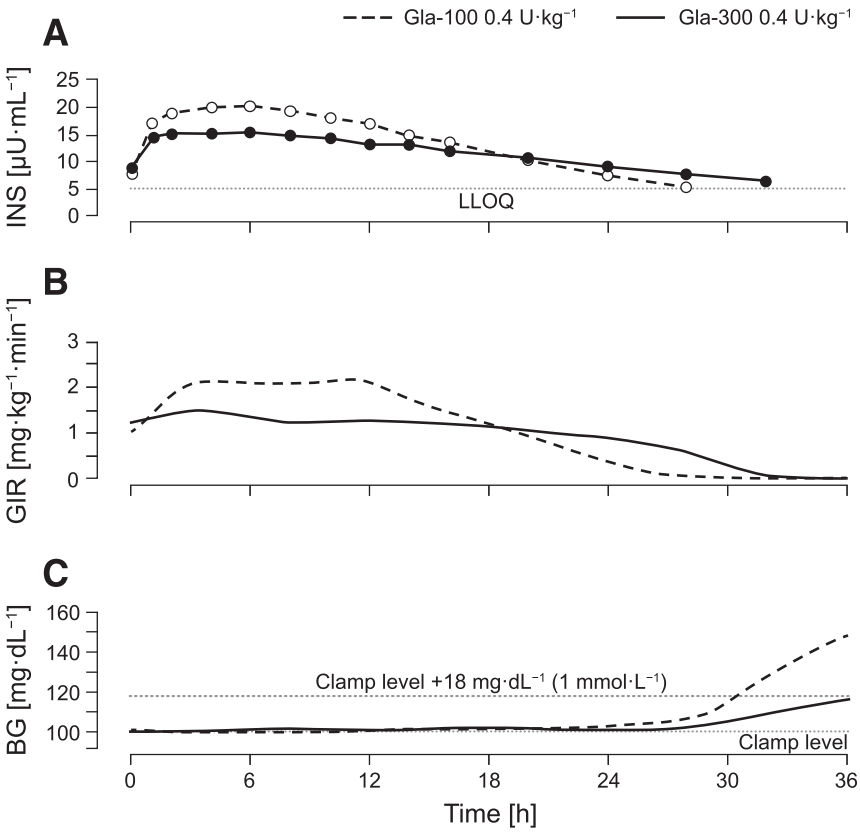

Figure 1—INS, GIR, and blood glucose profiles after multiple doses in steady state. Steady-state profiles of (*A*) mean INS (LLOQ = 5.02 units·mL^{-1}), (*B*) smoothed (LOESS factor 0.15) body-weight–standardized GIR, and (*C*) smoothed (LOESS factor 0.15) Biostator measured blood glucose, with threshold of blood glucose control ≤118 mg·dL^{-1}. All data shown from cohort 1; Gla-100 0.4 units·kg^{-1} versus Gla-300 0.4 units·kg^{-1}. BG, blood glucose.

PD

The GIR profiles with Gla-300 in steady state represented a stable, constant activity over 24 h, with a slow decline beyond this time (Fig. 1). After an equal dose of 0.4 units·kg^{-1}·day^{-1}, GIR was more evenly distributed with Gla-300 (Figs. 1 and 2) and remained at a higher level 24 h after dosing compared with Gla-100 (Fig. 1). Thus the GIR steady-state profiles of Gla-300 reflect the PK pattern with the lower swing in exposure (Table 1). Individual PD profiles are presented in Supplementary Figs. 2 and 3. With both Gla-100 and Gla-300, GIR was >0 at time zero. GIR-AUC was slightly less within 24 h after 0.4 units·kg^{-1}·day^{-1} Gla-300 than with the same dose of Gla-100 (point estimate of treatment ratio 0.73 [90% CI 0.56 to 0.94]), approaching a more equal level by 36 h after dosing on day 8 (point estimate of treatment ratio 0.85 [90% CI 0.70 to 1.03]) (Table 2). The more even and extended glucodynamic activity is also evidenced by longer $T_{50\%}$-GIR-$AUC_{0–24/36}$ with Gla-300 versus Gla-100 when administered at the same dose (0.4 units·kg^{-1}·day^{-1}) (Table 2 and Figs. 1 and 2). Euglycemia and blood glucose control within predefined target ranges were maintained for longer with Gla-300 than with Gla-100 after dosing on day 8 (Fig. 1 and Supplementary Tables 4 and 5), indicating that the rise in blood glucose with cessation of insulin activity was more gradual with Gla-300.

Safety

Gla-300 was generally well tolerated, and there were similar rates of adverse events

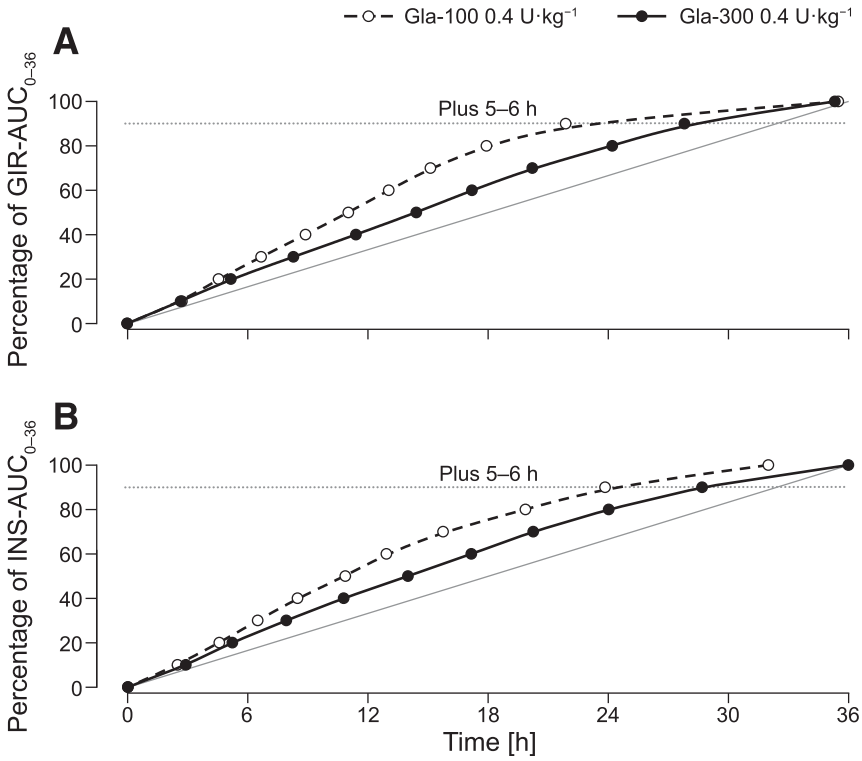

Figure 2—Cumulative metabolic effect and exposure after multiple doses in steady state. Mean time to a given percentage of (*A*) GIR-$AUC_{0–36}$ and (*B*) INS-$AUC_{0–36}$ during a 36-h euglycemic clamp in steady state after 8 days of once-daily dosing. All data shown from cohort 1; Gla-100 0.4 units·kg^{-1} versus Gla-300 0.4 units·kg^{-1}. Dotted gray horizontal line represents 90% of insulin effect or exposure. Solid gray line represents a theoretical perfect distribution.

between treatments. There were no serious adverse events. One participant was withdrawn after a non-drug-related adverse event after the first treatment period with Gla-100. No other withdrawals due to adverse events occurred.

CONCLUSIONS

The potential advantages of new Gla-300 are supported by the PK and PD profiles observed in a single-dose study (14) and confirmed by this steady-state study. Single-dose PK results have indicated that, compared with Gla-100, Gla-300 has a more gradual and prolonged release of insulin glargine from the SC depot at the injection site (14). We show that this, in steady state, translates into more constant PK profiles and more evenly distributed dynamic activity than Gla-100, with a prolonged duration of action beyond 24 h. However, it should be considered that the activity seen with Gla-300 beyond 24 h characterizes a pharmacological feature that is veiled within a stable, once-daily regimen. The more evenly distributed activity profile of Gla-300 over the full 36-h clamp period is attested by the somewhat lower glucose infusion within a 24-h interval compared with Gla-100. The results of this steady-state study indicate that Gla-300 is well suited for sustained, stable, and prolonged basal insulin supply.

Speculatively, based upon the more even PK and PD profiles, Gla-300 may be expected to confer a lower risk of hypoglycemia with equal or even tighter blood glucose control in a once-daily regimen compared with Gla-100. The actual effect of Gla-300 on these factors in clinical practice cannot be accurately inferred from a euglycemic clamp study, which is a controlled situation without the many variances associated with a real daily insulin regimen. However, the currently available results from the EDITION clinical trial program, which aims to evaluate Gla-300 in a variety of populations, demonstrate a benefit of Gla-300 over Gla-100 in terms of hypoglycemia (18,19). Further EDITION studies will continue to clarify the potential role of this promising new insulin glargine–based product.

Other ultra-long-acting insulin products have recently been approved or are in development, including degludec (12) and LY2605541 (13). Similarly to Gla-300 in the EDITION studies (18,19), both degludec (approved for use, e.g., in Europe and Japan) and LY2605541 (currently in development) report a lower risk of nocturnal hypoglycemia than Lantus (Gla-100), thus lending weight to the hypothesis that a smoother PK

Table 2—PD parameters after multiple doses in steady state

	Gla-100 0.4 units·kg^{-1}	Gla-300 0.4 units·kg^{-1}	Treatment ratio T/R (90% CI)	Treatment difference T − R (90% CI)
n	18	17‡		
GIR-$AUC_{0–24}$, mg·kg^{-1}*	2,449 (1,172)	2,028 (1,223)	0.73 (0.56 to 0.94)	
GIR-$AUC_{0–36}$, mg·kg^{-1}*	2,614 (1,182)	2,432 (1,379)	0.85 (0.70 to 1.03)	
GIR_{max}, mg·kg^{-1}·min^{-1}†	3.2 (2.6–3.8)	2.5 (1.8–3.4)	0.81 (0.68 to 0.97)	
$T_{50\%}$-GIR-$AUC_{0–24}$, h†	10.2 (9–11)	11.2 (10–13)		0.86 (−0.75 to 2.76)
$T_{50\%}$-GIR-$AUC_{0–36}$, h†	11.0 (9–12)	14.4 (11–16)		2.49 (1.05 to 4.77)

GIR_{max} is the maximum smoothed body-weight–standardized GIR (LOESS factor of 0.06). All data shown from cohort 1; Gla-100 0.4 units·kg^{-1} (reference) versus Gla-300 0.4 units·kg^{-1} (treatment). Data from cohort 2 are reported in Supplementary Table 3. R, reference; T, treatment. *Mean (SD). †Median (interquartile range). ‡One withdrawal prior to period 2.

profile confers a reduced hypoglycemic potential.

Assessing steady-state conditions based on a terminal half-life of ~19 h, insulin glargine blood concentrations are estimated to achieve steady state after 3 to 4 days with Gla-300. This is in line with results seen when 21^{A}-Gly-human insulin (metabolite M1) is measured separately (16), suggesting that responses to dose adjustments with Gla-300 can be well assessed within a week of treatment initiation, while allowing fast dose adaptations required for acute disease or unplanned physical activities. In contrast, longer terminal half-lives of 25 or 45–76 h, as observed for insulin degludec and LY2605541, respectively, may pose an issue for dose adjustment (20,21).

The longer duration of action of Gla-300 compared with Gla-100 could allow once-daily dosing for all people with diabetes and permit more flexibility in injection intervals, which may benefit people who are unable to administer their basal insulin at the same time each day. Clinical trials will be needed to investigate the possibility of enhanced flexibility in dosing intervals with Gla-300 and to determine whether this results in increased treatment satisfaction compared with Gla-100.

The strengths of this study include the fact that the euglycemic clamp was performed under steady-state conditions, which is a better reflection of a real-life scenario than a single-dose design, and the use of participants with type 1 diabetes who have negligible endogenous insulin production. The main limitation of this study, inherent to the experimental clamp setting, is the difficulty in extrapolating results directly to clinical practice. For example, the fact that the ratio (Gla-300/Gla-100) of total insulin activity over 24 h is lower than that of total insulin exposure must be interpreted in light of the apparent lower bioavailability of Gla-300 and the equal doses (0.4 units·kg^{-1}) given; due to these factors, a relatively greater proportion of the available Gla-300 would be required to dispose of hepatic glucose, resulting in less remaining insulin to demand glucose infusion. In addition, the fact that GIR is >0 at time zero may be viewed as a limitation, as it makes onset of action difficult to determine. However, this restriction is also a necessity of the controlled experimental setting, as at steady state with long-acting insulins, participants arrive at the unit on the day of the clamp with some remaining insulin effect from previous injections, requiring glucose infusion to reach the clamp target. Such limitations, however, do not impact upon the ability of this study to compare the pharmacological characteristics of insulin products assessed using the same methodology.

In conclusion, Gla-300 provides more even and prolonged PK and PD profiles compared with Gla-100, resulting in blood glucose control beyond 24 h. These findings merit further investigation in clinical trials to assess whether the PK and PD profiles of Gla-300 translate into clinical benefit.

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Author Contributions. R.H.A.B. contributed to the study conception and design and data analysis and interpretation and was responsible for the development of the manuscript. R.D., K.B., and A.L. contributed to the study conception and design, data analysis, and discussion and reviewed and edited the manuscript. T.J. and T.H. contributed to the study conception and design and data analysis and interpretation, performed the experiments, and reviewed and edited the manuscript. R.H.A.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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