Diabetes & Metabolism xxx (2017) xxx–xxx

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Original article

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

T.S. Bailey [a,*], J. Pettus [b], R. Roussel [c,d,e], W. Schmider [f], M. Maroccia [g], N. Nassr [f], O. Klein [h], G.B. Bolli [i], R. Dahmen [f]

[a] *AMCR Institute, 625 West Citracado Parkway Suite 112, Escondido, California 92025, USA*
[b] *University of California, San Diego, CA, USA*
[c] *Inserm U1138, Centre de Recherche des Cordeliers, 75006 Paris, France*
[d] *Université Paris Diderot, Sorbonne Paris Cité, 75013 Paris, France*
[e] *Diabetology, Endocrinology and Nutrition Department, DHU FIRE, Hôpital Bichat, AP–HP, 75018 Paris, France*
[f] *Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany*
[g] *Umanis, Levallois-Perret, 92300 France*
[h] *Profil, Neuss, Germany*
[i] *Department of Medicine, University of Perugia Medical School, Perugia, Italy*

ARTICLE INFO

Article history:
Received 28 July 2017
Received in revised form 4 October 2017
Accepted 8 October 2017
Available online xxx

Keywords:
Insulin degludec
Insulin glargine
Pharmacodynamic
Pharmacokinetic
Type 1 diabetes

ABSTRACT

Aim. – To compare steady state pharmacodynamic and pharmacokinetic profiles of insulin glargine 300 U/mL (Gla-300) with insulin degludec 100 U/mL (Deg-100) in people with type 1 diabetes.
Methods. – This single-centre, randomized, double-blind crossover euglycaemic clamp study included two parallel cohorts with fixed once-daily morning dose regimens. For both insulins participants received 0.4 ($n = 24$) or 0.6 U/kg/day ($n = 24$), before breakfast, for 8 days prior to the clamp. The main endpoint was within-day variability (fluctuation) of the smoothed glucose infusion rate (GIR) over 24 hours (GIR-smFL$_{0–24}$).
Results. – Gla-300 provided 20% less fluctuation of steady state glucose infusion rate profiles than Deg-100 over 24 hours at 0.4 U/kg/day (GIR-smFL$_{0–24}$ treatment ratio 0.80 [90% confidence interval: 0.66 to 0.96], $P = 0.047$), while at the dose of 0.6 U/kg/day the difference between insulins was not statistically significant (treatment ratio 0.96 [0.83 to 1.11], $P = 0.603$). Serum insulin concentrations appeared more evenly distributed with both dose levels of Gla-300 versus the same doses of Deg-100, as assessed by relative 6-hour fractions of the area under the curve within 24 hours. Both insulins provided exposure and activity until 30 hours (end of clamp).
Conclusion. – Gla-300 provides less fluctuating steady state pharmacodynamic profiles (i.e. lower within-day variability) and more evenly distributed pharmacokinetic profiles, compared with Deg-100 in a once-daily morning dosing regimen of 0.4 U/kg/day.

Introduction

The key component of the management strategy for people with type 1 diabetes (T1DM) and some with type 2 diabetes (T2DM) is basal and prandial insulin replacement. Although subcutaneous (SC) insulin replacement cannot fully mimic the physiology of endogenous insulin secretion [1], advances have been made over the last two decades, particularly with long-acting

Abbreviations: GIR-AUC$_{0–24}$, area under the GIR over time curve; GIR-smFL$_{0–24}$, fluctuation of the smoothed glucose infusion rate; LOESS, locally weighted regression in smoothing scatterplots; MAGE, mean amplitude of glycaemic excursions.

* Corresponding author.
E-mail address: tbailey@amcrinstitute.com (T.S. Bailey).

https://doi.org/10.1016/j.diabet.2017.10.001

basal insulin analogues that now exhibit flatter pharmacokinetic (PK) and pharmacodynamic (PD) profiles in a once-daily dosing regimen [2]. Smaller fluctuations (within-day variability) in PD activity, resulting from lower excursions of basal insulin plasma concentrations over the dosing interval, may better reproduce the physiology of basal insulin secretion in the fasting and inter-prandial state [1] and reduce hypoglycaemia risk.

Insulin glargine 300 U/mL (Gla-300) and insulin degludec 100 U/mL (Deg-100) are long-acting basal insulin products, both shown to have prolonged and more stable PK and PD profiles when compared with insulin glargine 100 U/mL (Gla-100) [3,4]. In phase 3 clinical treat-to-target trials, both Gla-300 and Deg-100 have been shown to be non-inferior to Gla-100 in terms of HbA_{1c} reduction, while resulting in less hypoglycaemia [5–7].

The aim of the present crossover study was to compare the PD and PK profiles of the same dose of Gla-300 and Deg-100 given in the morning, at two different dose levels at steady state, by using the euglycaemic clamp technique in people with T1DM.

Materials and methods

Participants

Males and females aged 18–64 years with a duration of T1DM > 1 year on a stable insulin regimen with total daily insulin dose < 1.2 U/kg were included. Participants were required to have a body mass index (BMI) between 18 and 30 kg/m^2, fasting C-peptide < 0.30 nmol/L, and $HbA_{1c} \leq 9.0\%$ (≤ 75 mmol/mol). Exclusion criteria included the presence or history of clinically relevant disease (other than T1DM), more than one episode of severe hypoglycaemia during the past 6 months, pregnancy, breast-feeding, and smoking more than 5 cigarettes or equivalent per day.

Study design and treatment

This single-centre, randomized, double-blind, two-treatment, two-period, two-sequence crossover euglycaemic clamp study (EudraCT Number 2015-004843-38) included two cohorts that each evaluated a different dose level of daily basal insulin (cohort 1, 0.4 U/kg/day [$n = 24$]; cohort 2, 0.6 U/kg/day [$n = 24$]) (Fig. S1; see supplementary data associated with this article online). Participants received treatment in the morning over 8 days with Gla-300 in the first treatment period and Deg-100 in the second treatment period, or vice versa (as assigned per randomization). There was a washout period of 8–26 days between treatment periods, during which participants used their pre-study insulin treatment.

After having washed out all prior basal and intermediate insulin products (washout of 72 hours for ultra-long-acting insulin products, 48 hours for long-acting insulin products, and 24 hours for intermediate-acting insulin products; participants taking short-acting insulin via an SC pump [continuous SC insulin infusion] discontinued their pump at least 30 minutes before the first administration of study medication), the first two doses of study medication were given in an initial in-house period in the mornings on days 1 and 2 to enable an immediate intervention by the medical personnel on-site in case of hypoglycaemia. This was followed by ambulatory on-site visits on days 3–7 in the mornings, during which further basal insulin doses were given by medical personnel, and a final in-house period from day 7 (evening) until day 9 (afternoon) during which the final 8th dose was given on day 8 in the morning and the clamp was initiated. On days 1–7 participants took variable doses of prandial insulin (insulin glulisine, administered in disposable pens for SC injection) at mealtimes as needed, in addition to the fixed daily basal insulin doses. The basal insulin dose on day 8 of each treatment period was given in fasting condition at approximately 08:00 h and followed by a 30-hour euglycaemic glucose clamp. Each treatment was administered subcutaneously in the periumbilical region with daily rotating change of the abdominal quadrants, as a single daily dose, in the mornings at approximately 08:00 h in the research unit by medically trained staff.

The glucose clamp setting was started during the night between days 7 and 8, approximately 8 hours before the last scheduled dosing of study treatment, to stabilize participants' blood glucose (BG) at the euglycaemic target level by the time of dosing (euglycaemia titration period). At this time (around midnight), participants were connected to the clamp device (ClampArt®, Profil, Neuss, Germany [8]). The last meal before the fasting period of the clamp procedure was dinner, given at approximately 7 pm on day 7. At this time, the last dose of prandial insulin was injected. Dinner had to be finished by 20:00 h (12 hours before dosing). During the euglycaemia titration period, participants received a variable intravenous infusion of insulin glulisine (a solution with 15 U insulin glulisine [100 U/mL] in 49 mL saline to which 1 mL of the participant's own blood was added to prevent insulin adhesion) and/or a variable glucose infusion (20%), to achieve and stabilize the BG target level of 5.5 mmol/L (100 mg/dL) ± 20%. The BG target level had to be stable within this range for at least 1 hour prior to dosing and the insulin glulisine infusion had to be discontinued at least 20 minutes before administration of study treatment in the morning on day 8. The euglycaemic clamp was then performed for up to 30 hours from dosing on day 8 with automated adaptations of the glucose infusion rate (GIR) every minute, but was stopped earlier if BG consistently exceeded 11.1 mmol/L (200 mg/dL) for 30 minutes in the absence of intravenous glucose infusion. After the end of the clamp, the participants were served a meal and resumed their pre-study insulin regimen. The study was performed in compliance with Good Clinical Practice, the Helsinki Declaration and local regulations. The protocol was approved by the Ethics Committee of the Regional Medical Council and The Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM), and all participants provided written informed consent.

Pharmacodynamic and pharmacokinetic assessments

The main PD endpoint in this study was the fluctuation (within-day variability) of the smoothed GIR curve over a 24-hour dosing period in steady state (GIR-$smFL_{0-24}$) (Fig. S2; see supplementary data associated with this article online). For this endpoint, the area of the individual smoothed GIR above and below the individual average GIR line is calculated, providing the mean amplitude of GIR fluctuations around the average GIR over 24 hours. This measure of within-day variability of PD activity in a euglycaemic clamp has been previously used to compare the within-day variability of basal insulins [4]. Other PD endpoints included area under the body weight standardized GIR curve within 24 hours (GIR-AUC_{0-24}), relative 6-hour fractions of GIR-AUC_{0-24}, maximum smoothed GIR (GIR_{max}), time to 50% of GIR-AUC_{0-24} ($T_{50\%}$-GIR-AUC_{0-24}), and duration of euglycaemia (defined as the time smoothed BG remained ≤ 5.8 mmol/L [≤ 105 mg/dL]).

PK endpoints of the study included area under the serum insulin concentration (INS) curves within 24 hours (INS-AUC_{0-24}), relative 6-hour fractions of INS-AUC_{0-24}, time to 50% of INS-AUC_{0-24} ($T_{50\%}$-INS-AUC_{0-24}), maximum INS (INS-C_{max}), time to INS-C_{max} (T_{max}), swing degree of INS fluctuation ($[C_{max} - C_{min}]/C_{min}$), and relative degree of fluctuation ($[C_{max} - C_{min}]/C_{av}$).

INS was determined using validated radioimmunoassays with a lower limit of quantification of 5.02 μU/mL for insulin glargine and 12 μU/mL for insulin degludec. As these assays are non-specific,

Please cite this article in press as: Bailey TS, 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 (2017), https://doi.org/10.1016/j.diabet.2017.10.001

there was a possibility of cross-reactivity (particularly to insulin glulisine, as this was infused during the euglycaemia titration period). The insulin glargine assay measured free serum parent insulin glargine and its active metabolites M1 and M2 as described previously [9], and the insulin degludec assay measured total serum insulin degludec (bound and unbound).

Safety

Safety assessments, performed in all participants, included adverse events (AEs), hypoglycaemic events (defined by self-monitored plasma glucose measurements and recorded in participants' diaries), local injection site reactions, vital signs, ECG recordings, and clinical laboratory evaluations.

Statistical analysis

Sample size calculations were based on the results of an earlier phase 1 Gla-300 study for 0.4 U/kg/day and 0.6 U/kg/day doses in steady state (Supplementary Methods and Table S1; see supplementary data associated with this article online) and used a maximum imprecision approach. In order to have the 22 evaluable patients estimated to be required per cohort for PK and PD, 24 patients were enrolled in each (48 patients in total).

Statistical analyses were performed separately for each dose cohort, comparing Gla-300 with Deg-100 treatment. Analyses included graphical presentations of PD and PK profiles, and descriptive statistics of PD and PK parameters by treatment and cohort. A linear mixed-effects model on log-transformed data was applied to estimate pairwise treatment ratios for GIR-smFL$_{0–24}$. A locally weighted regression in smoothing scatterplots (LOESS; smoothing factor of 0.15) technique using SAS® software (SAS Institute Inc., Cary, NC, USA) was used for the smoothing of GIR and BG records from ClampArt®.

Clamps defined in this study as having insufficient quality were excluded from PD analyses; these were clamps with a utility (percentage of operational time) of less than 85%, presumed failed dosing or a control deviation (average difference between measured BG and target BG) of more than 1.7 mmol/L (30 mg/dL) within the first 24 hours (post hoc criterion). However, if the other clamp of a participant had sufficient clamp quality, (e.g. a utility equal to or above 85%), it was included for the non-comparative analyses (descriptive statistics of PD parameters).

Results

Participants

In cohort 1 (0.4 U/kg/day), 22 male and 2 female participants with T1DM were randomized to treatment. One participant withdrew after treatment period 1 for personal reasons (not owing to an AE). In cohort 2 (0.6 U/kg/day), 24 male participants with T1DM were randomized to treatment. One participant was withdrawn owing to an AE that occurred during washout after treatment period 1 (right vestibular neuritis); this was considered unrelated to the study medication in cohort 2. The characteristics of participants in cohorts 1 and 2 are shown in Table 1 and Table S2 (see supplementary data associated with this article online), respectively.

Pharmacodynamics

A summary of the main PD parameters for cohort 1 and 2 are shown in Table 2 and Table S3 (see supplementary data associated with this article online), respectively. Four clamps were excluded from the PD analysis owing to insufficient clamp quality (3 based on low utility [1 in cohort 1 and 2 in cohort 2], 1 based on high control deviation in cohort 1) and 1 owing to a presumed failed dosing of Gla-300 leading to immediate BG escape in cohort 1.

Table 1
Participant characteristics (cohort 1).

Characteristic	Cohort 1 (0.4 U/kg/day)
Number	24
Sex	
Male	22
Female	2
Age, years	43.7 (10.2)
Diabetes duration, years	23.0 (10.3)
BMI, kg/m^2	25.4 (2.5)
HbA$_{1c}$, %	7.4 (1.0)
Insulin dose[a], U/kg/day, mean (SD) [min–max]	
Basal	0.34 (0.14) [0.2–0.9]
Prandial	0.33 (0.11) [0.2–0.5]
Total dose	0.67 (0.16) [0.4–1.2]
Basal insulin type prior to study, *n*	
NPH insulin	5
Insulin detemir	3
Insulin glargine	8
Pump insulin	8

Data are mean (SD) unless otherwise specified.
BMI: body mass index; NPH: neutral protamine Hagedorn; SD: standard deviation.
[a] At screening.

Table 2
Summary of the main pharmacodynamic parameters (cohort 1).

Pharmacodynamic parameter	Gla-300 (0.4 U/kg/day) *n* = 21	Deg-100 (0.4 U/kg/day) *n* = 24
GIR-smFL$_{0–24}$ [mg/min/kg][a]	0.38 (0.17)	0.46 (0.19)
GIR-AUC$_{0–24}$ [mg/kg]	1676 (1084)	1947 (1083)
GIR$_{max}$ [mg/min/kg]	1.95 (0.98)	2.19 (0.97)
T$_{50\%}$-GIR-AUC$_{0–24}$ [h]	12.60 (2.00)	12.79 (1.06)

All data shown are from cohort 1, data from cohort 2 are reported in Table S3 (see supplementary data associated with this article online). Data are mean (SD).
AUC: area under the curve; CI: confidence interval; GIR: glucose infusion rate; GIR-smFL$_{0–24}$: fluctuation of the smoothed GIR curve over 24 hours; SD: standard deviation.
[a] Treatment ratio (Gla-300/Deg-100): 0.80 (90% CI: 0.66 to 0.96), $P = 0.047$.

The main endpoint, the fluctuation of the smoothed GIR (GIR-smFL$_{0–24}$), was significantly lower with Gla-300 (mean [SD] of 0.38 [0.17] mg/min/kg) versus Deg-100 (0.46 [0.19] mg/min/kg) at the 0.4 U/kg/day dose level (Table 2 and Fig. 1A; treatment ratio 0.80 [90% confidence interval (90% CI): 0.66 to 0.96]; $P = 0.047$). At the 0.6 U/kg/day dose level, the difference in GIR-smFL$_{0–24}$ between insulins was not statistically significant, although it was numerically lower with Gla-300 than with Deg-100 (treatment ratio 0.96 [90% CI: 0.83 to 1.11]; $P = 0.603$) (Table S3 and Fig. S3A; see supplementary data associated with this article online). From visual inspection of the mean smoothed GIR over time curves, for both dose levels Gla-300 and Deg-100 started from similar GIR levels in the first 2 hours after dosing on day 8 and increased thereafter to a lower maximum activity (GIR$_{max}$) for Gla-300 versus Deg-100 at 12 to 14 hours. In the 0.4 U/kg/day cohort, activity returned for both insulins to a similar trough level at around 26 to 28 hours after dosing. The mean GIR-AUC $_{0–24}$ values were lower with Gla-300 than with Deg-100 at both dose levels (14% lower at 0.4 U/kg/day and 22% lower at 0.6 U/kg/day; Table 2 and Table S3; see supplementary data associated with this article online).

At steady state, relative 6-hour fractions of GIR-AUC$_{0–24}$ (Fig. 2A) appeared more evenly distributed with Gla-300 versus Deg-100 over the dosing interval of 24 hours in cohort 1 (0.4 U/kg/day). The mean 6-hour fractions of GIR-AUC$_{0–24}$ ranged from 18.2%

Please cite this article in press as: Bailey TS, 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 (2017), https://doi.org/10.1016/j.diabet.2017.10.001

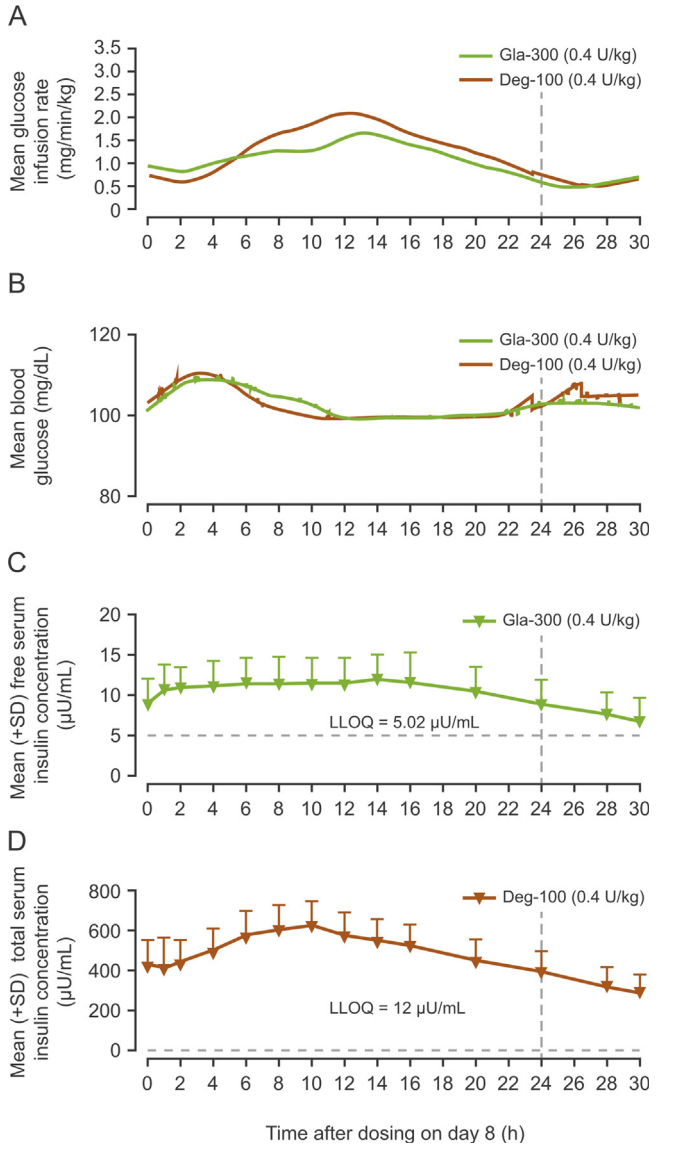

Fig. 1. Mean GIR (A), BG (B) and INS (C, D) profiles of Gla-300 and Deg-100 at the 0.4 U/kg/day dose level in steady state. For GIR and BG data a smoothing factor (LOESS factor 0.15) was applied. Validated radioimmunoassays were used to measure INS – LLOQ was 5.02 µU/mL for Gla-300 and 12 µU/mL for Deg-100 (Gla-300 assay measured serum parent glargine and active metabolites M1 and M2, Deg-100 assay measured bound and unbound serum insulin). Deviation of mean BG from target clamp levels reflects BG escapes in certain individuals. BG: blood glucose; GIR: glucose infusion rate; INS: serum insulin concentration; LLOQ: lower limit of quantification; SD: standard deviation.

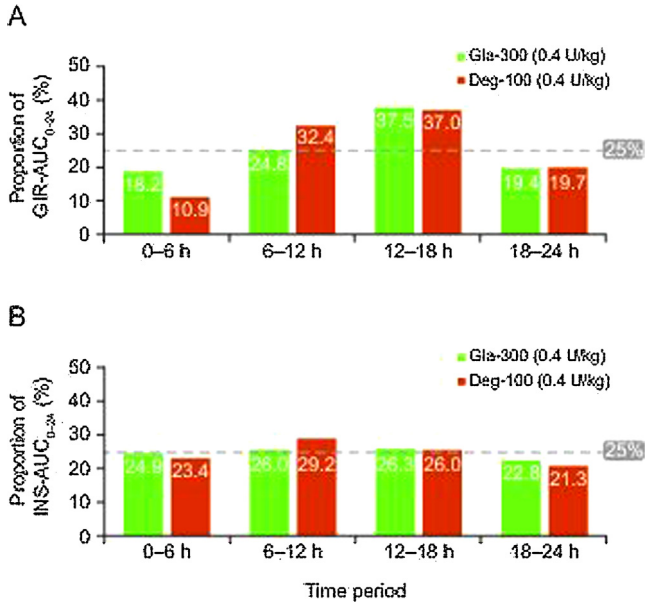

Fig. 2. Distribution of activity (A) and exposure (B) of Gla-300 and Deg-100 over 24 hours at the 0.4 U/kg/day dose level in steady state. Dashed grey lines represent the ideal constant activity of a basal insulin over 24 hours, with the same 25% of activity distributed in each of the four 6-hour periods. AUC: area under the curve; INS: serum insulin concentration; GIR: glucose infusion rate.

at 0–6 hours to 37.5% at 12–18 hours after dosing with Gla-300, whereas with Deg-100 the range was wider, being 10.9% at 0–6 hours and 37% at 12–18 hours. In cohort 2 (0.6 U/kg/day), the mean 6-hour fractions of GIR-AUC$_{0-24}$ displayed a similar pattern for both treatments (Fig. S4A; see supplementary data associated with this article online). The time to reach 50% of GIR-AUC$_{0-24}$ was similar for both insulins, at nearly 13 hours after dosing with 0.4 U/kg/day and around 12 hours after dosing with 0.6 U/kg/day (Table 2 and Table S3; see supplementary data associated with this article online).

Mean BG profiles at the 0.4 U/kg/day dose level are displayed in Fig. 1B. Mean duration of euglycaemia was similar for Gla-300 and Deg-100 at the 0.4 U/kg/day dose level, with smoothed BG remaining ≤ 5.8 mmol/L [≤ 105 mg/dL] for a mean of 29.3 hours for Gla-300 and 28.2 hours for Deg-100. Mean values for the duration of euglycaemia (≤ 5.8 mmol/L [≤ 105 mg/dL]) extended until clamp end (30 hours) for both Gla-300 and Deg-100 at the 0.6 U/kg/day dose (Fig. S3B; see supplementary data associated with this article online). Under steady state conditions, end of action could not be derived from these data as many patients under both insulins still had BG control 30 hours after dosing, which was the end of the clamp. Under both insulins, early temporary BG escapes were seen during some clamps, more at the 0.4 U/kg/day dose level than at the 0.6 U/kg/day dose level. These cases were made subject to exclusion in post hoc sensitivity analyses (one excluding 10 clamps with a precision [8] of > 10%, and one excluding 18 clamps with an initial escape of smoothed BG above 5.8 mmol/L [105 mg/dL]). Exclusion of these clamps did not greatly impact the main analysis as treatment ratios of the main endpoint (GIR-smFL$_{0-24}$) in cohort 1 became 0.77 ([90% CI: 0.62 to 0.96]; $P = 0.055$) and 0.75 ([90% CI: 0.58 to 0.99]; $P = 0.091$), for the two sensitivity analyses, respectively. The number of subjects remaining for these sensitivity analyses was reduced to 15 and 11 subjects (out of 24), respectively, which resulted in wider CIs and a subsequent loss of statistical significance.

Pharmacokinetics

A summary of the main PK parameters for cohorts 1 and 2 are shown in Table 3 and Table S4 (see supplementary data associated with this article online), respectively. One incomplete PK profile that resulted from early clamp termination due to presumed failed dosing (no change in INS level after dosing) was excluded from the PK analysis.

Consistently, insulin glargine PK profiles appeared overall more even than insulin degludec PK profiles at both the 0.4 (Fig. 1C and D) and 0.6 U/kg/day dose levels (Fig. S3C and S3D; see supplementary data associated with this article online). At both dose levels, insulin glargine demonstrated plateau-like INS profiles up to 16 hours post-dose, followed by a slow decline, whereas for insulin degludec the INS over time curve increased from the time of injection until a maximum concentration at 10 hours after dosing, before showing a similar slow decline. The geometric means of the relative degree of INS fluctuation over 24 hours were numerically

Please cite this article in press as: Bailey TS, 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 (2017), https://doi.org/10.1016/j.diabet.2017.10.001

Table 3
Summary of the main pharmacokinetic parameters (cohort 1).

Pharmacokinetic parameter	Gla-300[a] (0.4 U/kg/day) $n = 22$	Deg-100[b] (0.4 U/kg/day) $n = 24$
INS-C_{max} [μU/mL]	12.8 (25.2)	614 (20.4)
INS-AUC_{0-24} [μU.h/mL]	256 (27.2)	12100 (21.2)
$T_{50\%}$-INS-AUC_{0-24} [h], mean (SD)	11.82 (0.63)	11.43 (0.43)
T_{max} [h], median (min–max)	12.00 (2.00–20.00)	10.00 (6.00–12.00)
Swing degree of fluctuation	0.541 (110.7)	0.622 (48.1)
Relative degree of fluctuation (%)	40 (50.7)	46 (34.1)

All data shown are from cohort 1, data from cohort 2 are reported in Table S4 (see supplementary data associated with this article online). Data are geometric mean (CV%) unless otherwise specified; Swing degree of fluctuation = $(C_{max} - C_{min})/C_{min}$; Relative degree of fluctuation = $(C_{max} - C_{min})/C_{av}$.
AUC: area under the curve; CV%: coefficient of variation; INS: serum insulin concentration; SD: standard deviation.
[a] Free insulin glargine and active metabolites M1 and M2.
[b] Total (protein bound and free) insulin degludec.

smaller for insulin glargine (40% and 39%) than for insulin degludec (46% and 47%) at both 0.4 U/kg/day and 0.6 U/kg/day dose levels, respectively (Table 3 and Table S4; see supplementary data associated with this article online).

Similarly, the 6-hour fractions for INS-AUC_{0-24} appeared to show a more even distribution under insulin glargine versus insulin degludec, at both dose levels, but the between-treatment differences were small overall (Fig. 2B and Fig. S4B; see supplementary data associated with this article online). Exposure of both insulin glargine and insulin degludec was measurable until clamp end (30 hours) at both dose levels.

Safety

Gla-300 and Deg-100 were both well tolerated and there were no relevant differences in safety-related parameters (including hypoglycaemia) between treatments. Two serious AEs (right vestibular neuritis and an epileptic seizure) were reported during the study, both of which were outside the on-treatment period and classified by the investigator as not related to the study medication. For both insulins, the most frequent AE was documented symptomatic hypoglycaemia of mild and moderate intensity.

Discussion

This study was designed to compare the PD and PK profiles of two long-acting basal insulin products (Gla-300 and Deg-100) at steady state, when given in once-daily morning dosing regimens, in a head-to-head fashion using the euglycaemic glucose clamp technique. Gla-300 and Deg-100 have both previously been shown to have more favourable PK/PD profiles than Gla-100 [3,4].

The present study demonstrated that Gla-300 resulted in 20% less within-day variability (fluctuation) of the PD profile than Deg-100 at the same dose (0.4 U/kg/day). This dose appears slightly above the usual daily basal insulin dose of people with T1DM who participated in this study (Table 1). However, it is in the range of the dose of Gla-300 seen in a clinical trial of T1DM, which requires a ~ 17% increase versus Gla-100 [7]. At the higher dose of 0.6 U/kg/day, the difference in this measure of within-day variability between the two insulins was numerically in favour of Gla-300 although not statistically significant.

The same PD variability metric has been analysed in previous euglycaemic clamp studies comparing Gla-300 with Gla-100 [3], and Deg-100 with Gla-100 [4]. The study described by Becker et al. [3], applying the same smoothing factor as the current study, resulted in within-day GIR variability of 0.28 mg/min/kg for Gla-300 and 0.48 mg/min/kg for Gla-100, at the dose level of 0.4 U/kg/day [Sanofi data on file]. In the study comparing Deg-100 with Gla-100, the mean within-day GIR variability at a steady state dose of 0.4 U/kg/day was 0.25 mg/min/kg for Deg-100 and 0.39 mg/min/kg for Gla-100, although the smoothing applied on the GIR over time curve was the same [4]. Therefore, both basal insulins used in the current study have previously been shown to have lower levels of within-day GIR variability than Gla-100. It is tempting to speculate that the lower levels of within-day GIR variability of Gla-300 and Deg-100 compared with Gla-100 is one of the mechanisms by which Gla-300 [5,10] and Deg-100 [6,11] reduce the risk of hypoglycaemia in T1DM and T2DM.

Whereas within-day fluctuations in the GIR in a euglycaemic clamp setting indicate how stable and flat a basal insulin's metabolic activity is, continuous glucose monitoring (CGM) can be used to directly measure parameters of fluctuation in BG to evaluate consistency in glycaemic control of an insulin regimen, such as within-day variability of glucose levels or mean amplitude of glycaemic excursions (MAGE). Smaller within-day fluctuations, measured using CGM outside the context of a euglycaemic clamp study, can be linked with reduced risk of hypoglycaemia [12]. A previous CGM study comparing the diurnal glucose profiles of Gla-300 and Gla-100, taken in addition to prandial insulins in T1DM [12], reported a trend (not statistically significant) for lower within-day variability of glucose levels ('SD_w') under Gla-300 compared with Gla-100. The 24-hour glucose profiles showed fewer glycaemic excursions with Gla-300 than Gla-100, irrespective of morning or evening basal insulin dosing. Individual up-titration of insulin doses over 8 weeks for each dosing regimen resulted in a narrower range of daily glucose levels for Gla-300 than for Gla-100 based on mean 24-hour glucose profile, averaged for all participants on CGM in each group by time of day, with less nocturnal confirmed (< 54 mg/dL) or severe hypoglycaemia [12].

The current study showed that overall PD activity over 24 hours, as measured in the clamp setting by the area under the GIR over time curve (GIR-AUC_{0-24}), was lower with Gla-300 than with Deg-100 at both the 0.4 U/kg/day and 0.6 U/kg/day dose levels. This observation is well expected with Gla-300 and has already been reported when comparing equal doses (0.4 U/kg/day) of Gla-300 and Gla-100 in a euglycaemic clamp study with evening dosing [3]. The lower overall PD activity of Gla-300 is linked to its lower bioavailability, likely due to local degradation of Gla-300 in the SC depot during its release, which is protracted compared with Gla-100 [3], but with the longer half-life of Gla-300 not being associated with a risk of accumulation [13]. The PD activity of Gla-300 is not related to differences in molar potency compared with Gla-100, as both contain the same molecule (glargine), with the same main metabolite (M1) mediating insulin action [14], which is equipotent to human insulin [15]. The even insulin exposure with Gla-300, which remained constant for 16 hours followed by a slight decline, is significantly different from that of Gla-100, and is reached at lower bioavailability (as visualized by lower INS levels) especially in the first 12 hours after dosing, as previously reported [3]. The different bioavailability of Gla-300 and Gla-100 resulted in different daily basal insulin doses after titration in the EDITION trials in people with T1DM [7,10] and T2DM [5,16]. The lower PD activity with Gla-300 compared with Deg-100 observed in this study was expected from trials comparing Deg-100 with Gla-100 [17,18] and Gla-300 with Gla-100 [7,10]. However, as this was the first study to perform a head-to-head comparison of Gla-300 and Deg-100 in a euglycaemic clamp with morning dosing, it was reasonable to use the same unit dose for each insulin as an initial approach. Future studies will evaluate differences in within-day variability using different doses of the two insulins matched for equivalent glucose-lowering efficacy.

Please cite this article in press as: Bailey TS, 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 (2017), https://doi.org/10.1016/j.diabet.2017.10.001

The PD variability of insulin degludec vs. Gla-300 has been recently investigated in another euglycaemic clamp study by Heise et al. [19], claiming lower day-to-day and relative within-day variability in favour of degludec. The results of the Heise et al. study [19] appear to contrast with those presented here, despite the apparently similar study setting and clamp methodology. However, the study by Heise et al. [19] used a different degludec formulation (200 U/mL; Deg-200) and had a different objective (i.e. day-to-day variability) not addressed in the present study. Heise et al. [19] also calculated within-day variability, but in contrast to the present study the calculation was a post-hoc analysis and done with a relative estimate (i.e., GIR fluctuations given as a percentage of the individual mean GIR), rather than an estimate of absolute fluctuations (as in the present and previous studies [4]) that indicates excursions in metabolic activity over 24 hours as a mean amplitude in mg/min/kg. In addition, only PD data from the clamp have been published, whereas the present study presents PK and PD. Last but not least, the Heise et al. study [19] was performed with evening dosing, whereas the present study used morning dosing. This difference is important, as the same insulin dose may have different effects if given in the morning or evening owing to circadian variations of insulin sensitivity, as demonstrated for Gla-100 in T2DM [20]. A difference in the effect of morning and evening dosing has also been suggested in T1DM, by a lower difference in dose between Gla-300 and Gla-100 with morning versus evening dosing [7]. Morning rather than evening dosing with Gla-300 might also explain some differences in PD observed in the present study compared with previous studies of evening dosing with Gla-100 [3] or Deg-100 [4]. Importantly, both in the present study and in that of Heise et al. [19] there were individual clamps with transient hyperglycaemia after dosing, which appear to be more relevant in the central part of the 24-hour clamp in the Heise et al. study [19]. Although Heise et al. [19] report that sensitivity analyses excluding clamps with low glucose infusion confirmed the difference in the main endpoint, details of criteria for low glucose infusion are not published, and prolonged hyperglycaemia in a clamp that should be euglycaemic artificially dictates lower GIR down to zero, thereby artificially increasing GIR fluctuations (variability). Taken together, the above points suggest that the study of Heise et al. [19] does not prove lower day-to-day variability of degludec versus Gla-300 and additional investigations are needed to answer the question in euglycaemic clamp studies.

The present study also has limitations in addition to the strengths of its outcomes. The results of this study observed with morning dosing should be confirmed with further studies investigating evening dosing, ideally with doses of basal insulins that are based on the needs of individuals, instead of daily fixed doses. The clamp should be strictly euglycaemic, and insulin activity before SC insulin injection at time zero should be minimized. In general, the methodological approaches for studying PK/PD of long-acting insulins should be discussed in more depth and be validated.

As in the current euglycaemic clamp study in T1DM subjects, it has been shown for non-acylated basal insulins that GIR profiles reflect insulin exposures over time, usually with a delay of 1–2 hours [3]. Becker et al. [3] describe glargine exposure over 24 hours, with a smaller peak-to-trough value ('ΔINS') and swing degree of fluctuation ('Swing') with Gla-300 versus Gla-100, matching the lower within-day variability of GIR. The steady state PK characteristics of Deg-100 found in the current study are similar to previous descriptions in terms of exposure levels and profile pattern [4]; the exposure to Deg-100 increases slightly until a t_{max} around 8 to 10 hours after dosing followed by a steady decline. The maximum of the smoothed GIR plot follows a few hours later, at around 12 hours after dosing. However, overall the ability to compare PK parameters of Gla-300 and Deg-100 is limited by the fact that for Gla-300 it is possible to reliably measure the metabolically active fraction of circulating insulin ("free", not bound) with a radioimmunoassay, whereas for the acylated insulin degludec the radioimmunoassay identifies the "total" (albumin-bound + free, where free is a very small fraction). Therefore, in the latter case the assay may suggest only qualitatively, not quantitatively, the time profile of the active (free) fraction of degludec.

In the present study the 0.4 U/kg/day dose analysed is close to the average daily basal insulin dose of people with T1DM for Gla-300 in EDITION 4 [7] and EDITION JP 1 [10], and just above the dose for Deg-100 [17,18]. These data should illuminate what would happen to people with diabetes in real-world practice. Although the effect of a basal insulin in clinical practice cannot be fully predicted from the results of euglycaemic clamp studies, lower PD fluctuation of a basal insulin within a 24-hour period should provide smaller fluctuations in BG levels, with lower hypoglycaemic potential. In principle therefore, basal insulins with more stable 24-hour action profiles should allow similar glycaemic control with less hypoglycaemia or – since in theory they may be up-titrated more intensely – better glycaemic control with no hypoglycaemia increase. In this regard, both Gla-300 and Deg-100 reduce the risk of hypoglycaemia compared with Gla-100 [5,6,10,11]. The lower within-day variability of Gla-300 versus Deg-100 shown in the present study should be examined in additional future studies aimed at evaluating clinical impact in a less experimental setting.

At the 0.6 U/kg/day dose, the GIR fluctuation was still lower with Gla-300 than with Deg-100, although statistical significance was not reached. The reason why the between-treatment difference was significant at 0.4 but not 0.6 U/kg/day is not known, but a dose-response study focussing on within-day variability is required. However, the lower dose of 0.4 U/kg/day in this study is close to the usual daily basal insulin need in people with TIDM [7]. The 0.6 U/kg/day may be more relevant to people with T2DM and requires further evaluation in this population.

Conclusions

This study has demonstrated that Gla-300 has characteristics suitable for use as a once-daily basal insulin, with more evenly distributed PK profiles than Deg-100. At steady state in a euglycaemic setting with a morning dosing regimen, Gla-300 has 20% less within-day variability in its PD effect than Deg-100 does at the clinically relevant dose of 0.4 U/kg/day, while being similar at the dose of 0.6 U/kg/day. The potential implications of the differences reported here between Gla-300 and insulin degludec in people on basal insulin therapy with T1DM require additional evaluation, possibly with evening dosing and in people with T2DM, and should be confirmed in larger head-to-head phase 3 and real-world studies.

Role of the funding body

The clinical trial considered in this analysis was sponsored by Sanofi, Paris, France. Sanofi was responsible for the design and coordination of the trial, monitoring clinical sites, collecting and managing data, and performing all statistical analyses.

Author contributions

Raphael Dahmen and Oliver Klein developed the initial concept for this analysis. Timothy Bailey, Jeremy Pettus, Ronan Roussel, Wolfgang Schmider, Magali Maroccia, Nassr Nassr, Oliver Klein,

Please cite this article in press as: Bailey TS, 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 (2017), https://doi.org/10.1016/j.diabet.2017.10.001

Geremia Bolli and Raphael Dahmen participated in interpreting the findings as well as writing, reviewing and editing the manuscript.

Disclosure of interest

Timothy Bailey — Research Support: Abbott, Ambra, Ascensia, BD, Boehringer Ingelheim, Calibra, Companion Medical, Dexcom, Elcelyx, Glysens, Janssen, Lexicon, Eli Lilly, Medtronic, Novo Nordisk, Sanofi, Senseonics, Versartis, Xeris. Consulting Honoraria: AstraZeneca, Ascensia, BD, Calibra, Eli Lilly, Medtronic, Novo Nordisk, Sanofi. Speaking Honoraria: Abbott, Insulet, Medtronic, Eli Lilly, Novo Nordisk, Sanofi.

Jeremy Pettus — Advisory panel: Sanofi, Tandem Diabetes; speakers bureau: Boehringer Ingelheim, Dexcom.

Ronan Roussel — Advisory panel: Amgen, AstraZeneca, Sanofi, MSD, Eli Lilly, Janssen, Novo Nordisk, Physiogenex, Danone Research; Consultant: Sanofi.

Wolfgang Schmider, Nassr Nassr, Raphael Dahmen — Employees: Sanofi.

Magali Maroccia — Consultant: Sanofi.

Oliver Klein — Employee: Profil[1].

Geremia Bolli — Advisory panel: Sanofi; consultant: Novartis; speakers bureau: Eli Lilly.

Acknowledgements

The authors thank the study participants, trial staff, and investigators for their participation. The authors would also like to thank Dr Tim Heise (Profil) for valuable review and discussion of the manuscript content. Editorial and writing assistance was provided by Simon Rees, PhD, and Kerry Knight, PhD, of Fishawack Communications and was funded by Sanofi.

Appendix A. Supplementary data

Supplementary data (Figs. S1–S4, Tables S1–S4 and Supplementary Methods) associated with this article can be found, in the online version, at http://www.scincedirect.com and https://doi.org/10.1016/j.diabet.2017.10.001.

References

[1] Bolli 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] 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.
[4] Heise T, Hövelmann U, Nosek L, Hermanski L, Bøttcher 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.
[5] Ritzel R, Roussel 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.
[6] 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.
[7] Home PD, Bergenstal RM, Bolli GB, Ziemen M, Rojeski 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.
[8] Benesch C, Heise T, Klein O, Heinemann L, Arnolds S. How to assess the quality of glucose clamps? Evaluation of clamps performed with ClampArt, a novel automated clamp device. J Diabetes Sci Technol 2015;9:792–800.
[9] Bolli GB, Hahn AD, Schmidt R, Eisenblaetter 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.
[10] 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.
[11] Marso SP, McGuire DK, Zinman B, Poulter NR4, Emerson SS, Pieber TR, et al. Design of DEVOTE (Trial Comparing Cardiovascular Safety of Insulin Degludec vs. Insulin Glargine in Patients With Type 2 Diabetes at High Risk of Cardiovascular Events) – DEVOTE 1. Am Heart J 2016;179:175–83.
[12] Bergenstal RM, Bailey TS, Rodbard D, Ziemen 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. http://dx.doi.org/10.2337/dc16-0684.
[13] Monnier L, Owens DR, Bolli GB. The new long-acting insulin glargine U300 achieves an early steady state with low risk of accumulation. Diabetes Metab 2016;42:77–9.
[14] Steinstraesser A, Schmidt R, Bergmann K, Dahmen R, Becker RH. Investigational new insulin glargine 300 U/mL has the same metabolism as insulin glargine 100 U/mL. Diabetes Obes Metab 2014;16:873–6.
[15] Scholtz HE, Pretorius SG, Wessels DH, Venter C, Potgieter MA, Becker RH. Equipotency of insulin glargine and regular human insulin on glucose disposal in healthy subjects following intravenous infusion. Acta Diabetol 2003;40:156–62.
[16] 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.
[17] Heller S, Buse J, Fisher M, Garg S, Marre M, Merker L, et al. Insulin degludec, an ultra-long-acting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet 2012;379:1489–97.
[18] Mathieu C, Hollander P, Miranda-Palma B, Cooper J, Franek E, Russell-Jones D, et al. Efficacy and safety of insulin degludec in a flexible dosing regimen vs. insulin glargine in patients with type 1 diabetes (BEGIN: Flex T1): a 26-week randomized, treat-to-target trial with a 26-week extension. J Clin Endocrinol Metab 2013;98:1154–62.
[19] Heise T, Nørskov M, Nosek L1, 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.
[20] 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.

[1] Profil has received research funds from Adocia, Biocon, Dance Pharmaceuticals, Eli Lilly, Johnson & Johnson, Julphar, MedImmune, Mylan, Nordic Bioscience, Novo Nordisk, Poxel, Roche Diagnostics, Saniona, Sanofi, Senseonics, SkyePharma, Zealand Pharma.