Pharmacokinetics and pharmacodynamics of insulin glargine 300 U/mL in the treatment of diabetes and their clinical relevance

Abstract

Introduction: A more concentrated insulin glargine formulation, containing 300 U/mL (Gla-300) was approved in 2015 in the US and Europe for the treatment of diabetes mellitus in adults.

Areas covered: This review focuses on the pharmacokinetics (PK) and pharmacodynamics (PD) of Gla-300 from studies published up to May 2016. The clinical relevance of this new formulation will be addressed.

Expert opinion: Gla-300 was developed to produce a more flat and more prolonged PK/PD profile compared with insulin glargine 100 U/mL (Gla-100) in order to maintain effective glycaemic control and reduce the risk of hypoglycaemia. Compared to Gla-100, Gla-300 achieves lower and delayed peak concentrations with a PK exposure that is more stable and evenly distributed across a 24-h dosing interval. As a consequence, Gla-300 results in a consistent glucose-lowering effect with less variability over a 24-h dosing interval, which translates to a reduction in the rate of hypoglycaemia (particularly nocturnal events).

1. Introduction

Diabetes mellitus is a chronic condition currently estimated to affect 415 million people worldwide, and prevalence is expected to increase to 642 million people by 2040 [1]. Approximately 90%–95% of diagnosed cases are type 2 diabetes mellitus (T2DM) with type 1 diabetes (T1DM) comprising the remaining 5-10%. As T1DM tends to occur at a much younger age, those affected have a higher prevalence of complications than T2DM patients of a similar age [2].

2. Overview of current insulin therapy

Insulin remains the most effective means of consistent blood glucose control in diabetes, albeit limited by hypoglycaemia, weight gain and the need for parenteral administration. Subcutaneous injection of different formulations aims to replicate the endogenous pattern of insulin secretion observed in non-diabetic subjects as closely as possible without hypoglycaemia. Depending on their pharmacological profile following subcutaneous administration, the duration of action of insulin preparations can be classified as short-acting (prandial insulins), intermediate-acting, long-acting and longer-acting (basal insulins), or as premixed formulations.

Basal insulins are a fundamental component of insulin therapy for both T1DM and T2DM. Since 1946, Neutral Protamine Hagedorn (NPH) is the predominant basal insulin in clinical use globally. However, variability in absorption from the subcutaneous tissue, due to the need for re-suspension, as well as the time-action profile (peak activity 4-6 hours [h]) confers an increased propensity for between-meal and nocturnal hypoglycaemia [3,4]. In the 1980s, recombinant DNA technology enabled modifications to the insulin molecule resulting in soluble long-acting insulin analogues that did not require re-suspension before

administration; these showed improved pharmacokinetic (PK)/pharmacodynamic (PD) profiles compared with NPH [4]. Insulin glargine 100 U/mL (Gla-100, Lantus®; Sanofi, Paris, France) was the first approved in 2000, followed by insulin detemir (Levemir®; Novo Nordisk, Bagsværd, Denmark) in 2005. Both show a lower incidence of nocturnal hypoglycaemia compared with NPH due to improved time-action profiles and reduced day-to-day glucose variability. Glargine is administered once daily and detemir once or twice-daily. More recently, two longer-acting insulin formulations have been introduced, insulin degludec (Tresiba®, Novo Nordisk) in 2014 and insulin glargine 300 U/mL (Gla-300, Toujeo®, sanofi) in 2015. Development of a third longer-acting insulin, PEGylated lispro was recently discontinued due to safety concerns relating to elevated liver-function tests, changes in the lipid-profile, and increased liver fat [5,6].

3. Introduction to Gla-300

The development of new longer-acting insulin analogues has allowed for reduction in the peak-to-trough ratio coupled with a more prolonged and more consistent insulin coverage beyond 24 h, thus enabling glycaemic targets to be achieved with reduced risk of hypoglycaemia [7]. Extending the duration of insulin effect also improves flexibility around the time of dosing, simplifies insulin dose titration and allows a greater proportion of patients to reach their glycaemic targets [8]. This article reviews the pharmacological characteristics, and efficacy and tolerability of subcutaneous once-daily Gla-300 as basal insulin therapy in patients with T1DM or T2DM.

4. Chemistry

The active substance of Glar-300 is insulin glargine, which differs from human insulin in two ways: elongation of the C-terminal of the β-chain, due to the retention of two di-arginyl

molecules at position B30, and substitution of asparagine with glycine at position A21 (**Box 1**). These changes alter the isoelectric point of the molecule and improve its stability [9]. Insulin glargine binds specifically to the human insulin receptor with the same pharmacological effects as human insulin [10]. Gla-300 has the same molecular structure, metabolism and mode of protraction (forming subcutaneous precipitates) as Gla-100 (see *PK of Gla-300*).

5. Clinical Pharmacology of Gla-300

The clinical pharmacology data on Gla-300 is based on 6 randomised, Phase I studies (**Table 1**), comprising one single-dose study in healthy subjects [10], and 2 single-dose studies [11] and 3 multiple-dose studies [12-14] in subjects with T1DM. With the exception of one study that used continuous glucose monitoring (CGM) [14], all studies used the euglycaemic clamp technology over a period of 24 to 36 h after the last dose. In addition, a single phase II study in patients with T1DM provides information on within- and between-day variability in the glucose-lowering effect of Gla-300 [15].

6. Pharmacokinetics and metabolism of Gla-300

As the PK of Gla-100 is well described [16,17], PK assessment of Gla-300 was based on a comparison of Gla-300 with Gla-100.

6.1. Absorption

Insulin glargine is soluble at acidic pH (~4.5) and precipitates after subcutaneous injection into the neutral pH of the interstitial fluid, resulting in delayed absorption and a prolonged duration of action [17,18]. The pH-dependent precipitation and re-dissolution of insulin glargine is dependent upon the concentration of the injected solution [11,19]. This glargine-

specific phenomenon may result in a surface-dependent release, proportional to the volume (surface area) of the amorphous precipitate [11].

Compared with Gla-100, the subcutaneous injection volume for the same number of insulin units is reduced by two-thirds with Gla-300 thereby creating a more compact subcutaneous depot with a surface area that is about half that of Gla-100 (**Figure 1**). As a result, there is reduction in the dissolution rate of the subcutaneous precipitate, leading to an increased residence time in the subcutaneous tissue, and longer exposure to enzymatic inactivation by tissue peptidases [20-22]. This more gradual and prolonged release of Gla-300 leads to prolongation of action compared with Gla-100 [11-13]. A similar increase in residence time in the subcutaneous tissue and consequent reduction in bioavailability has been observed with other insulins (e.g. NPH and ultralente) that also rely on precipitation in the subcutaneous space to prolong their time action profile [23]. Due to the increased subcutaneous retention time and a lower bioavailability compared with equivalent doses of Gla-100 [10], a higher dose of Gla-300 may be required to achieve a similar glycaemic response.

Two single-centre, randomised, double-blind crossover studies evaluated single subcutaneous doses of Gla-300 compared with Gla-100, 0.4 U/kg in Japanese or European subjects with T1DM (see **Table 2** for doses). Both studies adopted the euglycaemic clamp procedure although using different glycaemic control devices (STG-22® and Biostator®, respectively) with a 5-20 day washout period between each of the treatment periods [11]. In European subjects, single doses of Gla-300 (0.4, 0.6 and 0.9 U/kg) resulted in a serum insulin glargine concentration (INS) profile that was flatter and more prolonged compared with Gla-100 (0.4 U/kg) during a 36 h clamp period [11] (**Figure 2**). Maximum serum concentration (C_{max}) was later than with Gla-100 (12-16 h versus 8-12 h), with reduced overall exposure (area under the INS time curve from time 0 to 36 h [INS-$AUC_{0–36h}$]) (**Table 2**). The median time to 50%

of insulin glargine exposure over the whole 36 h clamp period ($T_{50\%}$-INS-AUC_{0-36}) was also longer for Gla-300 than Gla-100 (15-19 h versus 13-14 h), indicating a more prolonged and more evenly distributed exposure profile. Results were generally similar in Japanese subjects (**Figure 2, Table 2**).

Multiple doses of Gla-300 at two dose levels (0.4 and 0.6 U/kg) and Gla-100 at 0.4 U/kg were administered to two cohorts of European patients (n=30) with T1DM over an 8-day period [12]. At steady state, the insulin concentration profile the 0.4 U/kg dose was more constant and more evenly distributed especially over the first 24 h of the 36 h clamp with Gla-300 compared with Gla-100 (**Figure 3**) [12]. Exposure of Gla-300 at 24-h (INS-$AUC_{0–24h}$) was 17% lower than with Gla-100. The prolonged exposure with Gla-300 was supported by the time to 50% of insulin exposure ($T_{50\%}$-INS-$AUC_{0–36h}$) being ~3 h longer for Gla-300 than Gla-100 during the full 36-h clamp period (~14 versus ~11 h) (**Table 3**). Gla-300 also showed less fluctuation in insulin exposure compared with Gla-100, as shown by a smaller perturbation (swing) in the concentration profile of <1 versus 1.8 for Gla-100.

6.2. Distribution

The estimated terminal median half-life of Gla-300 0.4 U/kg in subjects with T1DM is longer than that of Glar-100 (19 h versus 13.5 h) [12], as it is determined by the rate of absorption from the subcutaneous tissue and is independent of dose [24]. Based on this half-life, insulin glargine blood concentrations with Gla-300 are estimated to achieve steady state after 3 to 4 days, compared with 2 to 3 days with Gla-100 [25]. The longer half-life of Gla-300 results in longer availability of Gla-300, with levels still measurable in excess of 30 h after dosing (**Figure 3**).

6.3. Pharmacokinetic Variability

Within-day fluctuation and between-day reproducibility in insulin concentrations with Gla-300 at steady-state was investigated in a double-blind, randomised, two-treatment, two-period, crossover euglycaemic clamp study in subjects with T1DM (n=50) who were treated with 0.4 U/kg of Gla-300 as a standard cartridge formulation or a formulation with enhanced stability through the addition of polysorbate-20 [13]. A 24-h euglycaemic glucose clamp was carried out on the sixth day of treatment, after steady state had been achieved. There was low variability in insulin concentrations, with median cumulative exposure increasing linearly over the 24 h clamp period with an even distribution over each 12-h time period (**Figure 4**). The median bi-directional fluctuation in exposure around the average concentration over 24 h (11.3 μU/mL) was 3.3 μU/mL. Diurnal fluctuation in exposure (within-day variability) was low; the median peak-to-trough ratio of insulin concentration profiles was 1.8, with both the swing and peak-to-trough fluctuation being <1. Day-to-day reproducibility of exposure was high; the between-day within-subject coefficients of variation for total systemic exposure (INS-$AUC_{0–24h}$) and maximum insulin concentration (INS-C_{max}) were 17.4% and 33.4%, respectively. In summary, this study confirmed that Gla-300 provides predictable, evenly distributed 24-h coverage with low diurnal fluctuation in insulin concentrations and a high level of between-day reproducibility in insulin glargine exposure [13].

6.4. Metabolism of Gla-300

Insulin glargine mimics the physiology of human insulin. Similar to maturation of human insulin in β-cells, after subcutaneous injection, insulin glargine undergoes rapid transformation in the subcutaneous tissue to form 2 active metabolites with *in vitro* activity similar to that of human insulin, M1 (Gly^{A21}) and M2 (Gly^{A21}, des-Thr^{B30}) [26]. The M1 metabolite accounts for approximately 90% of the daily plasma insulin available [27,28].

Both metabolites have a very low affinity for the human insulin-like growth factor-1 receptor (IGF-1R) and lower mitogenic properties compared with the parent compound and similar to or lower than human insulin [29].

In patients with T1DM, the metabolites of Gla-300 and Gla-100 were quantified using liquid chromatography tandem mass spectrometry [25]. Gla-300 showed the same metabolism as Gla-100, with the M1 metabolite being the principal active moiety circulating in blood. Steady-state concentrations of M1 were dose dependent and achieved after 2 days for Gla-100 and 3-4 days for Gla-300, and were quantifiable up to 32 h and 36 h (clamp end), respectively (**Figure 5A**). M1 values for Gla-300 also showed a longer duration of action and a flatter PK profile compared with M1 profiles after Gla-100 (**Figure 5B**).

7. Pharmacodynamic Characteristics of Gla-300

The euglycaemic glucose-clamp technique is regarded as the gold standard for investigating PD profiles of insulin preparations [30]. Studies are usually conducted in patients with T1DM as they have no endogenous insulin secretion. The amount of glucose infused over time, expressed as glucose infusion rate (GIR), necessary to maintain blood glucose at the target blood glucose level, accurately reflects the PD effect of the insulin preparation [31].

7.1. Pharmacodynamic - Glucodynamic Profile of Gla-300

Following single subcutaneous doses of Gla-300 in European (0.4, 0.6 and 0.9 U/kg; n=24) and Japanese (0.4 and 0.6 U/kg; n=18) subjects with T1DM, the GIR profile was flatter and more prolonged than with Gla-100 (0.4 U/kg) during the 36 h clamp period [11] (**Figure 2**). The total insulin activity (area under the body-weight standardised GIR time curve from time 0 to 36 h [GIR-$AUC_{0–36h}$]) increased in a dose-dependent manner with Gla-300 (**Table 2**). The time to 50% of insulin activity (GIR-$AUC_{0–36h}$) was approximately 5 h longer for all Gla-

300 doses than for Gla-100 (~18 h versus ~13 h),especially for the 0.6 and 0.9 U/kg doses. In both studies, glucose utilisation was delayed, with maximum effect lower for Gla-300 at 0.4 and 0.6 U/kg compared with Gla-100 at 0.4 U/kg. Glucose-lowering activity was detected for up to 36 h with all doses of Gla-300.

In another study, multiple doses of Gla-300 0.4 and 0.6 U/kg and Gla-100 0.4 U/kg were administered over an 8 day period to two cohorts of European patients (n=30) with T1DM [12]. After dosing at 0.4 U/kg, the steady state GIR profile was more constant and more evenly distributed and remained at a higher level after 24 h with Gla-300 compared with Gla-100 (**Figure 3**) [12]. The maximum level of glucose utilisation (GIR_{max}) was significantly lower by 20% with Gla-300 at a dose of 0.4 U/kg (**Table 3**). The time to 50% of insulin activity (GIR-$AUC_{0–36h}$) was also longer for Gla-300 for both the 0.4 and 0.6 U/kg dose levels (~14 h) than for Gla-100 at 0.4 U/kg (11-12 h) during the 36-h clamp period. After the final dose on day 8, blood glucose was maintained at ≤105 mg/dL for longer with Gla-300 than Gla-100 at 0.4 U/kg (33 h versus 29 h). Similarly, during the 36-hour clamp period, blood glucose was more tightly controlled and was maintained at or below 110, 130 and 150 mg/dL, as well as the level of euglycaemia (≤105 mg/dL), for longer with both doses of Gla-300 than with 0.4 U/kg Gla-100. Following Gla-300 0.6 U/kg, blood glucose remained at or below 105 mg/dL for a median time of 35 h.

7.2. Variability in Glucose-Lowering Effect

Ideally, a long-acting insulin preparation should exhibit low diurnal variability (fluctuation) and low day-to-day variability (high reproducibility) to facilitate accurate dosing schedules. Day-to-day within subject variability in the glucose-lowering effect of Gla-300 at steady-state was investigated in a double-blind, randomised, two-treatment, two-period, crossover study in subjects with T1DM (n=50) who were dosed with 0.4 U/kg of Gla-300 [13]. A 24-h

euglycaemic clamp on day 6 showed that the cumulative glucose lowering effect of Gla-300 was linear over this period and essentially equivalent for the two 12 h periods reflecting the cumulative exposure of Gla-300 (see **Figure 4**)**.** The evenly distributed glucose-lowering effect of Gla-300 was confirmed by the AUC for GIR (AUC_{GIR}) across one 24-h dosing interval, with similar glucose-lowering effect over each of the four 6-h intervals. The median fluctuation in GIR (within-day PD variability) was 1.0 (interquartile range 0.8–1.1) mg/kg/min, and the within and between-subject coefficient of variation in GIR-AUC_{0-24} was 35% and 43%, respectively.

24-h glucose variability was assessed using CGM in a single-centre, 2-sequence, 2-period, open label cross-over study comparing Gla-100 and Gla-300 in 20 Japanese people with T1DM, [14]. CGM was performed over 3 days at the end of screening and each of the treatment periods over a 4 week period. Glucose variability over 24 h was measured as the absolute AUC above and below the individual average plasma glucose value on the second day of CGM. The 24 h glucose variability was not statistically different between Gla-300 and Gla-100 (treatment ratio 0.96; 90 % CI 0.79–1.16), with similar variability during day (treatment ratio 1.01; 90% CI 0.84-1.21) and night (treatment ratio 0.94; 90%, CI 0.69-1.27) [14].

Variability was further investigated in a multicentre, 16-week, open-label, randomised, parallel group, phase II study in patients with T1DM (n=59) who received either Gla-300 or Gla-100 once daily in combination with rapid-acting mealtime insulin, with crossover between morning and evening injections [15]. Each treatment period was 8 weeks, with insulin dose titration over the first 6 weeks and fixed doses for the final 2 weeks during which the CGM data were evaluated. Gla-300 injected either in the morning or the evening showed lower within- and between-day glucose variability and a similar percentage time in the sensor

target glucose range (4.4-7.8 mmol/L, primary outcome) compared with Gla-100 [15] (**Figure 6**). When morning and evening injection periods were combined, within-subject blood glucose variability parameters were consistently lower with Gla-300: total standard deviation lower by 7.4%, within-day variability by 5.4%, variability between daily means by 14.3% and variability between days for the same time of day by 7.2% (all non-significant). The reduced within-subject variability with Gla-300, irrespective of morning or evening administration, indicates that some flexibility in injection times is possible.

8. Pharmacokinetic and Pharmacodynamic Characteristics of Gla-300 in Special Patient Populations

8.1. Children and Adolescents

As the PK and PD profile of Gla-300 in children and adolescents (<18 years) has not been studied the use of Gla-300 is not recommended in this patient population [24,32]. A dedicated randomised controlled trial comparing Gla-300 and Gla-100 in children and adolescents aged 6-17 years with T1DM (EDITION JUNIOR) has commenced enrolment [33].

8.2. Elderly patients

While post-hoc analyses from phase III trials do not indicate differences in safety and efficacy profile among patients ≥65 years [34], caution is recommended when Gla-300 is administered to elderly patient's ≥65 years. A dedicated randomised controlled trial comparing Gla-300 and Gla-100 in elderly patients with T2DM (EDITION SENIOR) has completed enrolment [35].

8.3. Renal or Hepatic Impairment

Due to progressive deterioration of renal function, insulin requirements may be reduced in elderly patients (aged ≥65 years) [24]. In addition, insulin requirements may a need to be reduced in younger patients with renal impairment (because of reduced insulin elimination) or hepatic impairment (because of reduced insulin metabolism and reduced capacity for gluconeogenesis) [24]. As there is a lack of data concerning the effects of renal or hepatic impairment on the PK of Gla-300, patients with renal or hepatic impairment receiving Gla-300 may require more frequent glucose monitoring and dose adjustment [32].

9. Clinical efficacy

9.1. Phase II studies

As described in section 7.2, a single phase II trial in adults with T1DM (n=59) [15] showed that the proportion of time spent within a glucose range of 4.4–7.8 mmol/L in the last 2 weeks of each treatment period (primary endpoint) did not differ significantly with Gla-300 or Gla-100 [least squares mean difference 0.75 %; 95 % CI –3.61 to 5.12]. However, pooled average glucose profiles showed that Gla-300 provided more stable glucose levels throughout the day than Gla-100 for both morning and evening injections, with less glucose excursion, and lower between-day glucose variability (**Figure 6**).

9.2. Phase III studies

The EDITION trial programme, comprising 6 randomised, controlled, open-label, multicentre, treat-to-target, 6-month Phase IIIa trials compared the efficacy and safety of Gla-300 with Gla-100 (**Table 5**) [20,21,36-39]. Each trial was extended by 6 months to investigate long-term safety [40-45]. Two trials in patients with T2DM (EDITION 1 and 2) evaluated flexible dosing intervals during the 6-month extension period in a subgroup of

patients, with patients asked to take their evening doses of Gla-300 3 h earlier or later than their chosen injection time on at least 2 days per week, or continue with their fixed 24-h dosing intervals [46]. The trials used the same weekly dose titration to achieve the target fasting plasma glucose (FPG) concentration of 4.4–5.6 mmol/L (80–100 mg/dL) in T2DM or 4.4–7.2 mmol/L (80–130 mg/dL) in T1DM (i.e., treat-to-target approach). Gla-300 and Gla-100 were administered once-daily in the evening except in EDITION 4 where they were given in the morning or evening.

As expected, all trials confirmed the non-inferiority of Gla-300 and Gla-100 for the change in HbA1c from baseline to the end of the 6-month treatment period (**Table 4**). In general, FPG was lowered by a similar extent with Gla-300 and Gla-100, with a statistically significant difference in favour of Gla-100 observed in one trial (EDITION 3). Across the trials, changes in variability in pre-injection SMPG, and the 8-point SMPG profile were generally similar in patients receiving Gla-300 and those receiving Ga-100 [20-22]. In two sub-studies, a flexible Gla-300 dosing regimen did not compromise glycaemic control (HbA1c and FPG) or safety (hypoglycaemia) versus the fixed dose regimen [46]. In EDITION 4, the risk of hypoglycaemia was not affected by the timing of insulin glargine administration (i.e. morning or evening injection).

In all trials, hypoglycaemic events were categorised according to the American Diabetes Association definitions [47], as severe (requiring assistance from another individual) or confirmed symptomatic or asymptomatic hypoglycaemia (i.e. plasma glucose levels of ≤70 mg/dL or ≤3.9 mmol/L). Nocturnal hypoglycaemia was defined as confirmed hypoglycaemia events occurring in a 6 h time period from 00:00 h to 05:59 h. The percentage of patients experiencing ≥1 confirmed (blood glucose ≤70 mg/dL) or severe (American Diabetes Association definition) nocturnal hypoglycaemic event was assessed over a range of time

periods (week 9 to month 6 [main secondary endpoint in EDITION 1, 2 and 3], baseline to week 8, baseline to month 6 and baseline to month 12).

In general, Gla-300 was associated with a lower risk of nocturnal hypoglycaemia than Gla-100 in T2DM patients previously on insulin therapy, while the treatment difference in risk of nocturnal hypoglycaemia between week 9 and month 6 (the key secondary endpoint in the three largest trials) did not reach statistical significance in insulin-naïve patients with T2DM [mean reduction of 24% from baseline to 6 months] or in patients with T1DM. Lower rates of hypoglycaemia with Gla-300 versus Gla-100 were apparent even during the titration period (i.e. baseline to week 8) in most trials. Two trials in insulin-experienced patients (EDITION 1 and 2) also showed a significantly lower risk of hypoglycaemia during the day. A patient-level meta-analysis of three trials (EDITION 1, 2 and 3) involving more than 2,400 patients with T2DM showed that over the 6-month treatment period, annualised rates of confirmed or severe hypoglycaemia were 31% lower with Gla-300 than with Gla-100 during the night (2.10 vs. 3.06 events per patient-year; rate ratio 0.69; 95 % CI 0.57–0.84) and 14% lower during the day (15.22 vs. 17.73 events per patient-year; rate ratio 0.86; 95 % CI 0.77–0.97) [22]. Corresponding rates at 1 year were 2.0 versus 2.4 events per patient-year (rate ratio 0.82; 95 % CI 0.67–0.99) and 13.7 versus 14.1 events per patient-year (rate ratio 0.97; 95 % CI 0.87–1.09) [22]. Overall, these results indicate that the PK and PD properties of Gla-300 translate into clinically relevant benefits.

In most trials, weight gain tended to be less with Gla-300 than Gla-100 (~0.26 kg difference in T2DM; ~0.56 kg in T1DM) [10], reaching statistical significance at the end of treatment in four trials (EDITION 2, 4, JP1 and JP2). The mechanism responsible for this reduced weight gain with Gla-300 compared to Gla-100 is not known. Mean total daily insulin dose was also consistently higher with Gla-300 than Gla-100 (range 10-18%). The higher dose requirements

are consistent with the 17% lower 24-h exposure of Gla-300 compared with Gla-100 at fixed, equal doses (0.4 U/kg) [12] and may be attributable to the lower bioavailability of Gla-300 [10].

For a more thorough discussion of the phase III clinical trial data for Gla-300, the reader is referred to recent comprehensive reviews [48-50].

10. Clinical advantages and disadvantages of Gla-300

10.1. Advantages

The different formulation of insulin glargine in Gla-300 results in an improved PK/PD profile with a longer duration of action and less variable plasma insulin exposure, compared with Gla-100. The 6 randomised trials show a similar efficacy and safety profile, but importantly, a lower incidence of hypoglycaemic events with Gla-300 compared with Gla-100, and only a slight decrease in body weight gain with Gla-300 despite a 10-18% increase in insulin dose.

10.2. Disadvantages

From a clinical perspective, Gla-300 has only been compared with Gla-100 and comparative studies with other long- and longer-acting insulins such as insulin detemir and insulin degludec would help to determine the place in therapy for this new formulation of insulin glargine. Moreover, there are a number of limitations of the completed Phase III EDITION trials. These include the open-label design, the relatively short duration (6-12 months) and the limited generalisability of the results to other populations with diabetes.

The 10-18% higher insulin dose required with Gla-300 compared with Gla-100 is an important consideration that needs to be balanced against the lower risk of hypoglycaemia, minimal decrease in weight gain and a greater degree of flexibility compared with the

original insulin glargine formulation. Therefore, cost-effectiveness may be a defining issue in the uptake of this new insulin analog. At present, no such data has been reported for Gla-300.

11. Safety and tolerability

In all clinical trials conducted to date, Gla-300 was safe and well tolerated, with no differences between Gla-300 and Gla-100 with respect to the incidence of adverse events (AEs). The most common AEs were hypoglycaemia, allergic reactions, injection site reaction, lipodystrophy, pruritus, rash, oedema and weight gain [32]. The sub-studies in EDITION 1 and EDITION 2 indicated that the use of adjusted dose intervals did not affect the safety profile of Gla-300 [46]. The Gla-300 formulation showed the same good local tolerability as the Gla-100 formulation following subcutaneous administration [10].

Gla-100 and Gla-300 are not bioequivalent and are not directly interchangeable [24]. Therefore, switching from Gla-100 to Gla-300 can be done on a unit-to-unit basis, although a higher Gla-300 dose (approximately 10-18%) may be needed to achieve target ranges for FPG levels. It is recommended that when switching from Gla-300 to Gla-100, the dose should initially be reduced (by approximately 20%) to reduce the risk of hypoglycaemia before subsequent dose titration [24].

Blood samples for measurement of insulin antibodies were collected during phase III trials at baseline, at weeks 4 and 12, and at month 6 [21]. At baseline, a similar percentage of Gla-300 and Gla-100 patients were positive for anti-insulin antibodies (AIAs) in T1DM (61.7% and 53.6%, respectively), as well as T2DM (41.6% and 37.7%) [10]. Throughout the 6-month treatment period, the percentage of AIA-positive patients slightly increased in T1DM patients, in both the Gla-300 and Gla-100 groups, and remained similar in all T2DM patients. Among the AIA-positive patients, the percentage of those with antibodies cross-reacting with

human insulin was similar between treatment groups for T1DM and T2DM. No major differences over time or between treatment groups were observed for antibody titre. In all of the studies, formation of AIAs was similar between Gla-100 and Gla-300 and had no impact on the efficacy and safety profiles of either basal insulin.

12. Regulatory affairs

Gla-300 was approved for the treatment of diabetes mellitus in adults by the Food and Drug Administration (FDA) in February 2015 and by the European Medicines Agency (EMA) in April 2015. Gla-300 was licensed in Japan in 2015.

13. Conclusion

Gla-300 is a new long-acting insulin glargine formulation that has the same molecular structure, mode of protraction (forming precipitates) and metabolism as Gla-100.

The PK and PD trials described here, show that glycaemic control in T1DM was maintained for a longer duration with Gla-300 than Gla-100 (33 h versus 29 h), and insulin exposure was more stable and evenly distributed across a 24-h dosing interval with a high level of between-day reproducibility compared to Gla-100.

The Phase III EDITION clinical trials indicated that Gla-300 provides a similar level of glycaemic control to Gla-100 but with a lower rate of hypoglycaemic events, particularly nocturnal episodes. Due to its lower bioavailability, a higher daily dose of Gla-300 may be required to achieve a similar glycaemic response. Taken together, the available data suggest that Gla-300 represents an attractive alternative to use of Gla-100 for many patients.

14. Expert opinion

The development of new longer-acting basal insulins like Gla-300 represents an important advance in insulin therapy for the management of patients with diabetes. Variability in the absorption and the modest half-lives of current once-daily basal insulin therapies provide challenges in achieving day long (both nocturnal and interprandial) glycaemic control while minimising the risk of hypoglycaemia.

Gla-300 was developed to provide a flatter and more prolonged PK/PD profile compared with Gla-100, in order to maintain effective glycaemic control while reducing the risk of hypoglycaemia. The studies described here indicate that Gla-300 achieves peak concentrations that are lower and delayed, and has a PK exposure that is more stable and evenly distributed than Gla-100. The improved PK profile results in an even distribution of glucose-lowering effect across a 24-h period, with reduced variability in glucose lowering within and between days.

The improved PK/PD characteristics of Gla-300 are supported by findings from Phase III clinical trial programme showing similar glycaemic control to Gla-100 albeit with a significantly lower risk of nocturnal hypoglycaemia and similar or significantly less daytime hypoglycaemia. This reduced risk of hypoglycaemia with Gla-300 is a potentially important finding, given that clinical concern relating to hypoglycaemia is often a barrier to effective dose adjustment and attainment of target glycaemic control. The lower risk of hypoglycaemia with Gla-300 observed during the titration period may also allow for a smoother, safer and more reliable insulin titration [20-22], leading to improved confidence in increasing the dose for both physicians and patients with diabetes [20].

The need for a 10-18% higher insulin requirement with Gla-300 versus Gla-100 is related to its reduced bioavailability following subcutaneous administration. The economic consequences of this higher dose requirement will need to be balanced against the reduced propensity for hypoglycaemia. Moreover, despite the higher doses of Gla-300, weight gain did not increase significantly, indeed a modest, but statistically significant reduction in body weight gain was observed in several of the Phase III clinical trials. The difference in body weight (~0.25 kg) between the two two insulin formulations at 6 months is relatively minor. Gla-300 appears to be associated with greater flexibility in time-of-day dosing, which may make it easier to achieve optimal insulin titration in clinical practice. This is likely to be of greatest benefit to those patients who find it difficult to adhere to the precise timing of injections required. Further studies will be required to verify the findings observed in these short-term studies, and results from additional studies in the elderly and children are expected over the next few years.

Besides Gla-300, insulin degludec has been approved in many countries. As both of these insulin therapies show a similar long-action profile of more than 36 h, each has the potential to become a central insulin therapy for patients with T1DM and T2DM. The lack of comparative trial between these two new therapies means that indirect comparisons will need to be made in the future. In this respect, a recent network meta-analysis compared Gla-300 with other basal insulin therapies used for patients with T2DM [51], and suggested that Gla-300 is associated with glycaemic control comparable to available basal insulin comparators (degludec and detemir), has a similar risk of symptomatic hypoglycaemia versus other therapies (degludec, detemir and NPH), and a significantly lower risk of nocturnal hypoglycaemia compared with NPH and premixed insulin.

In summary, the available evidence suggests that Gla-300 represents an important advance in insulin treatment for patients with diabetes.

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15. Box 1. Drug summary

Drug name Insulin glargine injection 300 units/mL (Toujeo)

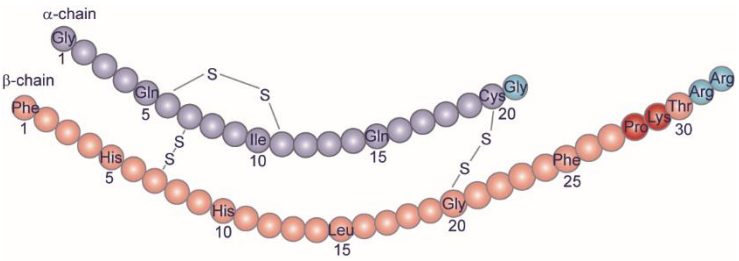
Phase Approved by FDA in February 2015 and by EMA in April 2015

Indication Treatment of diabetes mellitus in adults

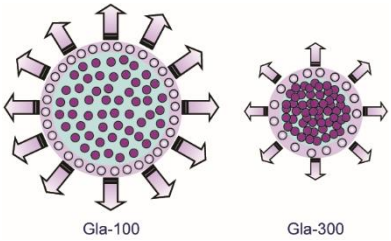
Pharmacology description Long-acting recombinant insulin analog

Route of administration Subcutaneous injection

Chemical structure



Depot: Gla-300 forms a compact subcutaneous depot with a smaller surtace area to produce more gradual and prolonged release compared with Gla-100



Pivotal trial (s) EDITION 1 [36], EDITION 2 [20], EDITION 3 [37], EDITION 4 [21], EDITION JP1 [38] and EDITION JP2 [39]

Table 1 Summary of PK/PD phase I and II trials of Gla-300

Authors, year	Population	N	Design	Main objectives	Euglycaemic clamp (Device, duration)
Single dose, Phase I					
PKD10086 [10]	Healthy volunteers	24	R, CO	Bioequivalence	✓ (Not known)
Single dose, Phase I					
Shiramoto 2015 [11]	T1DM (Japanese)	18	R, DB, CO	PK/PD	✓ (STG-22, 36 h)
Shiramoto 2015 [11]	T1DM (European)	24	R, DB, CO	PK/PD	✓ (Biostator, 36 h)
Steady state, Phase I					
Becker 2015 [12]	T1DM (European)	30	R, DB, CO	PK/PD	✓ (Biostator, 36 h)
Becker 2015 [13]	T1DM (European)	50	R, DB, CO	Bioequivalence	✓ (Biostator, 24 h)
Jinnouchi 2015 [14]	T1DM (Japanese)	18	R, OL, CO	PK/PD, CGM	x (CGM)
Steady state, Phase II					
Bergenstal 2014 [15]	T1DM	59	R, OL, CO	Glucose control	x (CGM)

CGM, continuous glucose monitoring; CO, crossover; DB, double blind; OL, open label; PK, pharmacokinetic; randomised,

Table 2 PK and PD characteristics after a single dose in (**A**) European and (**B**) Japanese patients with T1DM

	Gla-100 dose (U/kg)	**Gla-300 dose (U/kg)**	
	0.4	**0.4**	**0.6**
(A) European (n=15-22)			
INS-C_{max}, µU/mL	15.3 ± 6.0	**8.9 ± 2.9**	**9.3 ± 2.8**
INS-$AUC_{0–36}$, µU·h/mL	318 ± 109	**195 ± 89**	**206 ± 105**
$T_{50\%}$-INS-AUC_{0-36}, h	13 (12–15)	**15 (12–19)**	**17 (14–20**
INS-T_{max}, h	12 (8–12)	12 (8–14)	**12 (12–18**
GIR-$AUC_{0–36}$, mg/kg	1725 ± 920	**631 ± 590**	**1118 ± 10**
GIR_{max}, mg/kg/min*	2.2 ± 0.9	**1.6 ± 1.1**	1.5 ± 0.9
$T_{50\%}$-GIR-$AUC_{0–36}$, h	12 (11–13)	**17 (12–24)**	**17 (14–23**
(B) Japanese (n=15-18)			
INS-C_{max}, µU/mL	17.3 ± 4.8	**10.9 ± 3.4**	**13.8 ± 7.1**
INS-$AUC_{0–36}$, µU·h/mL	370 ± 101	**251 ± 92**	**326 ± 156**
$T_{50\%}$-INS-$AUC_{0–36}$, h	14 (12–15)	**17 (13–19)**	**18 (16–18**
INS-T_{max}, h	8 (2–12)	**16 (12–16)**	**14 (8–16)**
GIR-$AUC_{0–36}$, mg/kg	1859 ± 1085	**990 ± 1233**	**1591 ± 17**
GIR_{max}, mg/kg/min*	2.2 ± 0.8	**1.2 ± 1.0**	**1.8 ± 1.3**
$T_{50\%}$-GIR-$AUC_{0–36}$, h	13 (10–15)	**17 (14–21)§**	**18 (15–21**

All data are mean ± SD or median (interquartile range) for $T_{50\%}$-INS-AUC_{0-36}, INS-T_{max}, $T_{50\%}$-GIR-$AUC_{0–36}$
in bold indicate a statistically significant difference between Gla-300 and Gla-100 0.4 U/kg ($p<0.05$ or < 0.1

glargine 100 U/mL; Gla-300, insulin glargine 300 U/mL; INS, insulin glargine concentration; INS-C_{max}, max
INS-$AUC_{0–36}$, area under the concentration versus time curve from time 0 to 36 h; INS-T_{max}, time to INS-C_{ma}
of INS-$AUC_{0–36}$

Table 3 PK and PD parameters at steady state after multiple doses of Gla-300 and Gla-100 0.4 U/kg [12]

	Gla-100 0.4 U/kg (n=17-18)
INS-C_{max}, µU/mL	**23.4 ± 8.4**
INS-$AUC_{0–36}$, µU·h/mL	438 ± 167
$T_{50\%}$-INS-$AUC_{0–36}$, h	**10.9 (10–12)**
INS-$t_{1/2}$, h	13.5 ± 6.9
ΔINS, µU/mL*	15 (11–18)
Swing¶	1.8 (1.3–2.3)
GIR-$AUC_{0–36}$, mg/kg	2,614 (1,182)
GIR_{max}, mg/kg/min	3.2 (2.6–3.8)
$T_{50\%}$-GIR-$AUC_{0–36}$, h	11.0 (9–12)

All data are mean ± SD or median (interquartile range) for $T_{50\%}$-INS-$AUC_{0\text{-}36}$, ΔINS, Swing, GIR_{max}, $T_{50\%}$-G

*INS-C_{max} − INS-C_{24}.¶ (INS-C_{max} − INS-C_{24})/INS-C_{24}.

INS-C_{max}, maximum serum insulin concentration; INS-$_{t1/2}$; terminal half-life of serum insulin concentration; I
concentration versus time curve from time 0 to 36 hours; GIR_{max}, maximum smoothed body-weight–standard

The values in bold indicate a statistically significant difference between Gla-300 and Gla-100 0.4 U/kg.

Table 4 Summary of findings from randomised, open-label 6-month Phase III clinical trials comparing Gla-3

Study population	Study name	No. patients	HbA1c reduction with Gla-300 vs. Gla-100, ETD (%)	FPG reduction with Gla-300 vs. Gla-100, ETD (mmol/L)	Hypoglyca reduction)[a]
					At any tim of day[b] ([c])
Type 2 diabetes: Insulin-experienced patients					
On BB insulin + OADs	EDITION 1	807 [36]	-0.00%; non-inferior	0.09	↓**7%** (↓4%)
On basal insulin + OADs	EDITION 2	811 [20]	-0.01%; non-inferior	0.19	↓**10%** (↓9%
On basal insulin + OADs	EDITION JP2	241 [39]	0.04%; non-inferior	0.04	↓14% (↓16%
Type 2 diabetes: Insulin-naive patients					
On OADs	EDITION 3	878 [37]	0.04%; non-inferior	**-0.39**	↓12% (↓14%
Type 1 diabetes					
On BB insulin	EDITION 4	549 [21]	0.04%; non-inferior	0.19	0% (↓2%)
On BB insulin	EDITION JP1	243 [38]	0.13%; non-inferior	0.4	↓1% (↑1%)

The values in bold indicate a statistically significant difference between Gla-300 and Gla-100 ($p<0.05$)

BB, basal-bolus; ETD, estimated treatment difference; OADs, oral antidiabetic therapy; RAI, rapid-acting ins

[a]Patients experiencing ≥1 confirmed (blood glucose ≤70 mg/dL [≤3.9mmol/L]) or severe hypoglycaemic eve

[b]Between baseline and month 6.

[c]Between week 9 and month 6 (key secondary endpoint in EDITION 1, 2 and 3). The time period was chosen temporary alteration of the risk of hypoglycaemia following a switch from a known therapy (in most cases G insulin.

Figure 1: Mechanism of slower release from subcutaneous tissue of Gla-300 compared with Gla-100 **(A)** Curve illustrating how the smaller injection volume of Gla-300 translates to a smaller surface area in depot injection **(B)** Curve illustrating the concentration dependent release capacity of Gla-300 which is released more slowly than Gla-100 as the release rate is proportional to the surface area of the depot. Dp/dt indicates the glargine dispersal rate over time

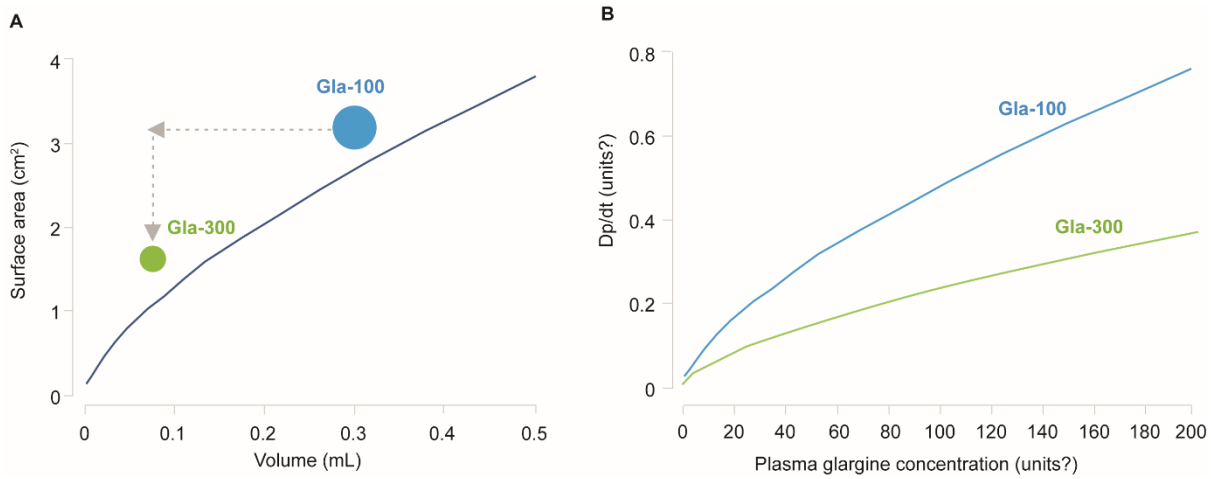


Figure 2 Median insulin (INS) concentration profiles (LLOQ = 5.02 µU/mL) (**A**), and smoothed (LOESS fac standardised glucose infusion rate profiles (**B**), with Gla-300 and Gla-100 following single dose administratio patients with T1DM. Reprinted from [11] with permission of John Wiley and Sons.

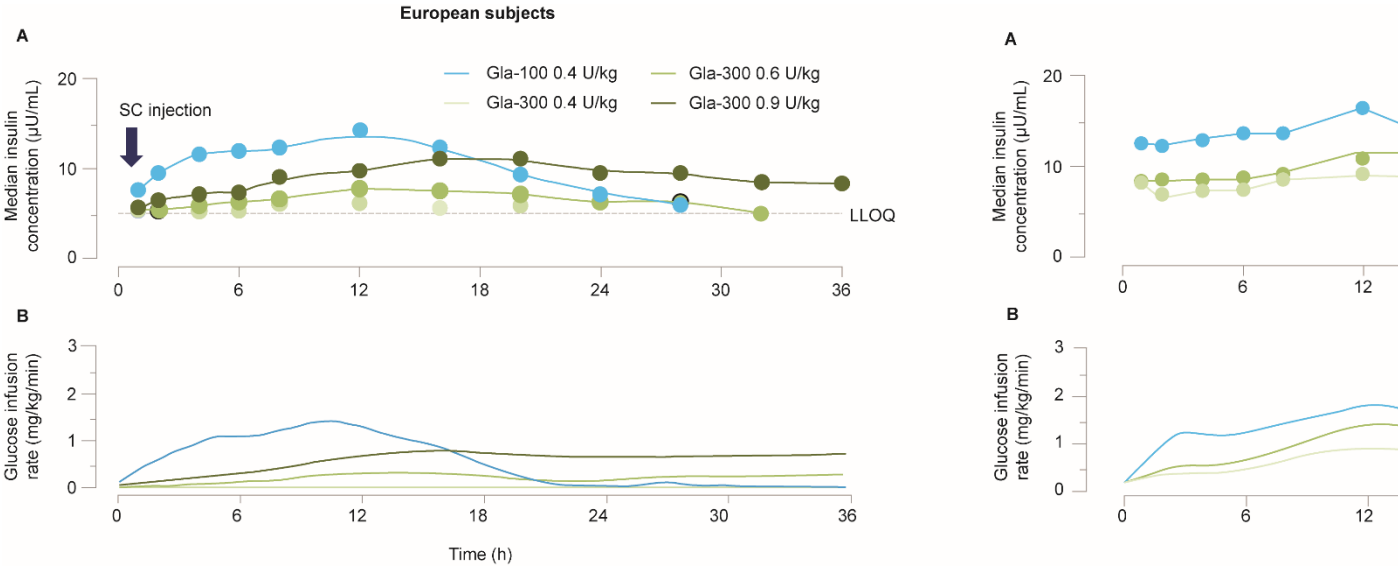
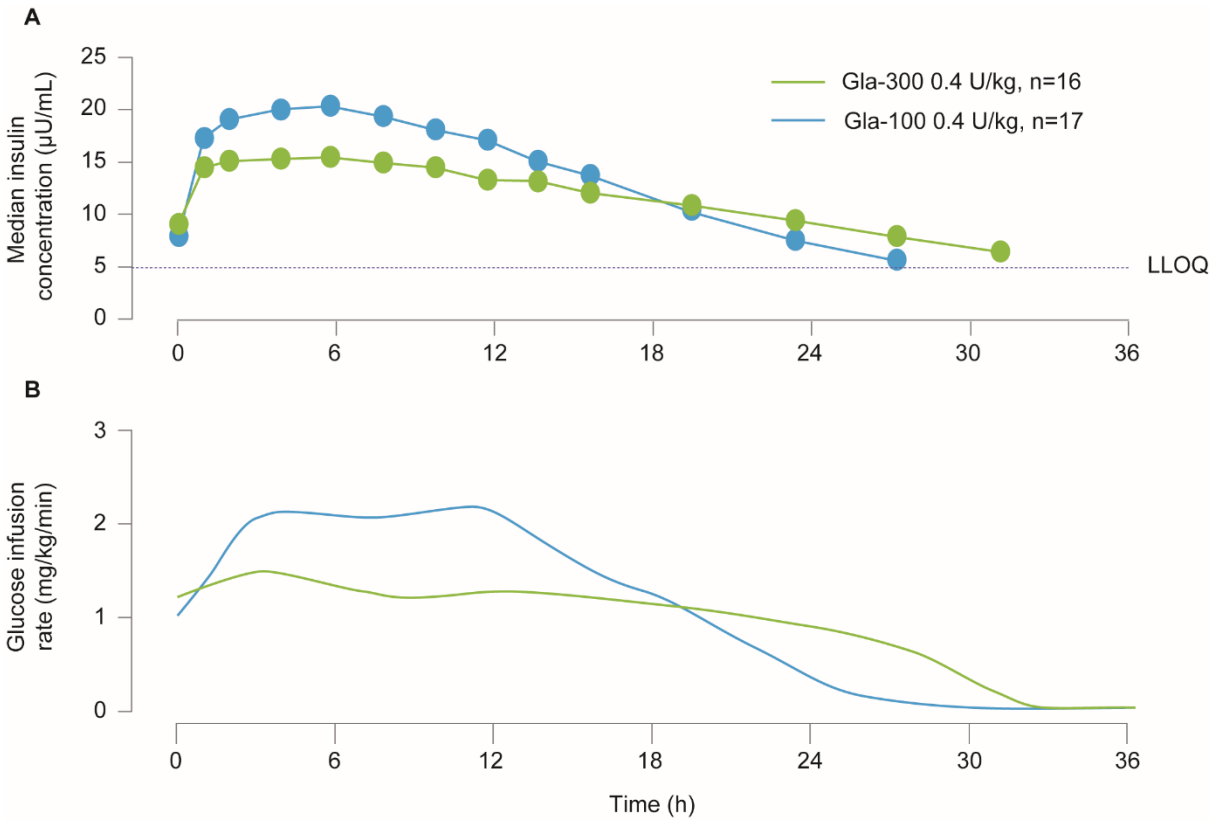


Figure 3 Mean insulin concentration (**A**), smoothed body weight standardised glucose infusion rate (**B**), and smoothed blood glucose measures (**C**) with Gla-300 and Gla-100 0.4 U/kg at steady state following 8 days of once-daily administration in subjects with T1DM (n=30). Thirty-six-hour mean blood glucose profiles during this clamp study. Reproduced from [12] with permission from American Diabetes Association.



BG, blood glucose; Gla-100, insulin glargine 100 units/mL; Gla-300, insulin glargine 300 units/mL; LLOQ, lower limit of quantification.

Figure 4 Pharmacokinetic and pharmacodynamic profiles for Gla-300 at steady state, by treatment period [13]. Profiles of (**A**) mean (standard deviation) serum insulin concentration (INS), lower limit of quantification (LLOQ) = 5.02 µU/mL. Two individual far outside values excluded (one in period 1, h 14 and one in period 2, h 8) ; and (**B**) Mean smoothed (LOESS factor 0.06) body-weight-standardised glucose infusion rate (GIR). in a crossover euglycaemic study of Gla-300 0.4 U/kg in 50 patients with T1DM. The percentage contribution of each 6 hour interval to the total AUC_{GIR} is shown in the Figure. Reprinted from [13] with permission of John Wiley and Sons.

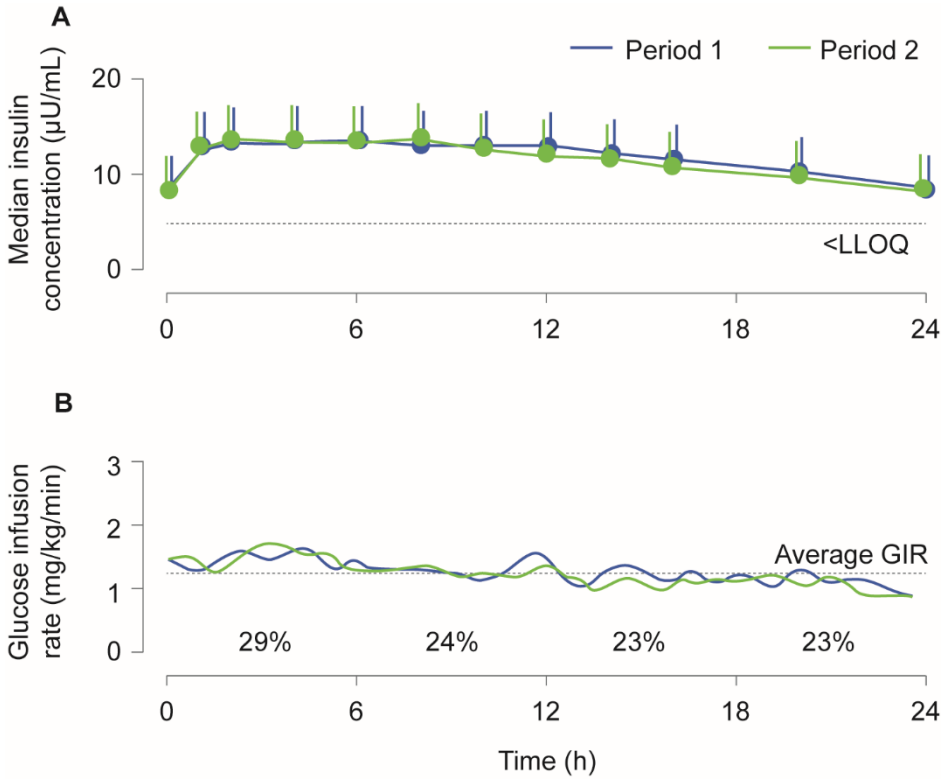


Figure 5 A) Median trough levels of M1 with an exponential regression of the data. The two Gla-100 reference groups are combined as a weighted average of the medians. **B)** M1 profiles at steady state. Reprinted from [25] with permission of John Wiley and Sons.

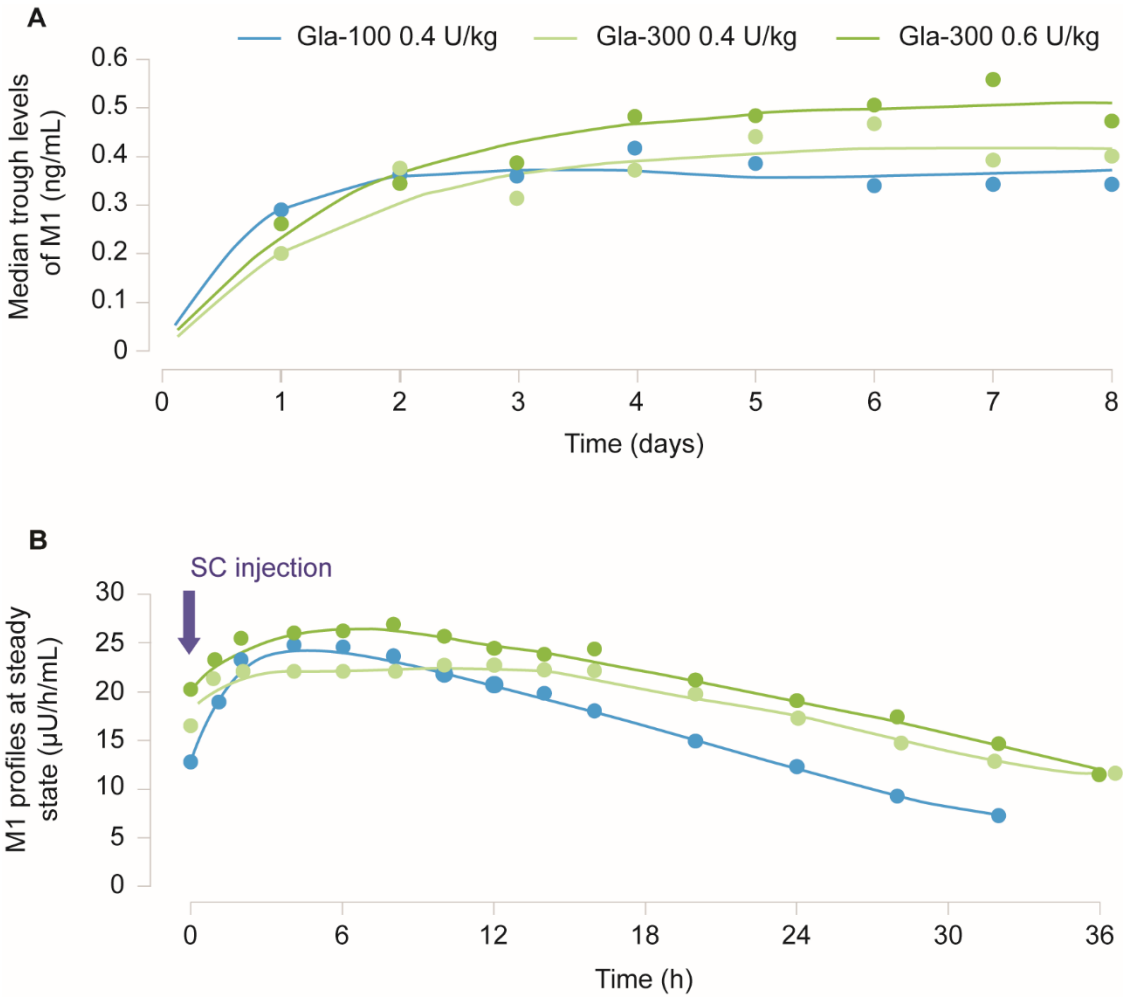


Figure 6 Mean 24-h glucose profiles with Gla-300 vs Gla-100 when administered in the morning or evening

treatment period (continuous glucose monitoring population; pooled data period A + B) [15]