U300 Insulin Glargine: A Novel Basal Insulin for Type 1 and Type 2 Diabetes

Journal of Pharmacy Technology
2015, Vol. 31(5) 234–242
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sagepub.com/journalsPermissions.nav
DOI: 10.1177/8755122515584193
pharmatech.sagepub.com

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Abstract

Objective: To review clinical efficacy and safety of insulin glargine 300 units/mL (Gla-300), a novel high-concentration basal insulin. **Data Sources:** A MEDLINE search was performed to identify relevant articles published 1960 through February 2015 using the search term glargine 300. Published abstracts from conference proceedings of the American Diabetes Association 74th Scientific Sessions were identified. **Study Selection and Data Extraction:** Human studies that evaluated pharmacokinetics, efficacy, or safety of Gla-300 were included. **Data Synthesis:** Six trials investigated efficacy and safety of Gla-300; 3 of 6 trials were available in abstract form only. The EDITION group of trials compared Gla-300 to insulin glargine 100 units/mL (Gla-100) in several populations. These included subjects with type 1 diabetes continuing mealtime insulin and subjects with type 2 diabetes on basal and mealtime insulin, basal insulin and oral antidiabetic drugs (OADs), and with no prior insulin use. Three studies were multinational including 2 studies exclusive to Japanese participants. Each clinical trial was an open-label, multicenter, randomized study with 6 to 12 months of follow-up. Gla-300 demonstrated similar reductions in HbA_{1c} compared to Gla-100. Basal insulin requirements increased by 11% to 17% with Gla-300 without excessive weight gain. Rates of overall hypoglycemia were similar with Gla-300 compared to Gla-100; however, 16% to 38% less nocturnal hypoglycemia was observed in type 2 clinical trials. **Conclusions:** Gla-300 in combination with mealtime insulin or OADs has shown comparable glycemic control with higher insulin dose requirements versus Gla-100, and may induce less hypoglycemia in patients with type 2 diabetes.

Keywords

insulin glargine U300, insulin glargine 300, glargine 300, Gla-300, basal insulin, concentrated insulin, diabetes, hypoglycemia

Introduction

Diabetes is both a significant and growing health concern affecting an estimated 382 million people worldwide.¹ There are 29.1 million people living with diabetes in the United States, and the prevalence is expected to increase 21.8% by the year 2035.^{1,2} Optimal glycemic control is paramount to reduce the risk of long-term microvascular and macrovascular complications including retinopathy, neuropathy, nephropathy, myocardial infarction, and stroke.^{3–5}

Insulin is the oldest and among the most efficacious diabetes treatments to date. Patients with type 1 diabetes mellitus (T1DM) require a combination of basal and mealtime insulin. In type 2 diabetes mellitus (T2DM), basal insulin should be considered as second-line therapy for patients who remain uncontrolled with oral antidiabetic drugs (OADs) or as first-line combination therapy in patients with very poor glycemic control.^{4,5} Pharmacokinetic properties of basal insulin products are described in Table 1.

The most common and significant adverse effects of insulin are hypoglycemia and weight gain.⁹ Fear of hypoglycemia

can be a barrier to initiating therapy and achieving optimal glycemic control with insulin. Hypoglycemia can negatively affect quality of life while severe hypoglycemia can be immediately life-threatening.⁴ Weight gain can promote or worsen obesity and contribute to insulin resistance.³ Patients with severe insulin resistance may require high doses of insulin, necessitating multiple injections to administer large volumes of insulin. Patients requiring large insulin doses may benefit from concentrated insulin formulations. Concentrated insulin allows administration of smaller volumes per dose and may reduce the total number of daily injections.^{10,11} Until recently, regular U-500 insulin

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Table 1. Pharmacokinetic Profiles of Basal Insulins⁶⁻⁸.

Type of Insulin	Onset	Peak (hours)	Duration (hours)
Intermediate-acting			
NPH	2-4 hours	4-8	8-12
Long-acting			
Degludec ^a	10-12 hours	—	>42
Detemir	2 hours	—	14-24
Glargine U-100	4-5 hours	—	22-24
Glargine U-300	6 hours	—	36

Abbreviation: NPH, neutral protamine Hagedorn.

^aNot currently approved by the US Food and Drug Administration.

was the only concentrated insulin.¹⁰ However, there are serious safety concerns with U-500 insulin. Life-threatening dosing errors have occurred due to lack of a U-500 syringe or availability of a U-500 insulin pen.¹² More recently, ultra-long-acting concentrated insulin analogs have been a target for advancement in diabetes therapy.

Basal insulin analogs, insulin glargine 100 units/mL (Gla-100) and insulin detemir, have represented clinically relevant improvements over previous intermediate- and long-acting insulin products. Basal insulin analogs induce less frequent hypoglycemia, provide more consistent insulin absorption, and produce a less pronounced peak compared to Neutral Protamine Hagedorn (NPH) insulin. Despite these improvements, optimal characteristics are still desired and include reduced peak-to-trough ratio, prolonged activity in all patients, reduced incidence of weight gain, and lower hypoglycemia risk.¹³ Insulin degludec (IDeg) is a recently developed novel ultra-long-acting basal insulin analog (currently available in Europe, Japan, and Mexico) with a flatter pharmacokinetic profile and less within-person variability compared to Gla-100. IDeg has demonstrated effective glycemic control with less hypoglycemia compared to other basal insulins. The unique duration of action greater than 42 hours allows more flexible dosing of the once daily insulin.¹⁴ The US Food and Drug Administration (FDA) denied the approval of IDeg requiring dedicated cardiovascular outcomes trial data.¹⁵ A 5-year study comparing cardiovascular safety of IDeg to Gla-100 in subjects with T2DM is currently underway with anticipated completion in 2018.¹⁶

Insulin glargine is an acidic solution that forms micro-precipitates following subcutaneous administration from which dissolution occurs slowly.¹⁷ The concentration of insulin glargine was thought to be inversely related to the redissolution rate. Therefore, insulin glargine 300 units/mL (Gla-300) was developed to provide more consistent insulin absorption and a longer duration of action than its predecessor, Gla-100.¹⁸ The FDA approved Gla-300 for adults with type 1 and type 2 diabetes in February 2015.¹⁹ Approval by the European Medicines Agency (EMA) is pending at the time of this writing.²⁰

Literature Search

A MEDLINE search was completed to identify relevant articles published 1960 through February 2015 using the search term glargine 300. Published abstracts from conference proceedings of the American Diabetes Association 74th Scientific Sessions were identified through a bibliography distributed by the manufacturer of Gla-300. All human studies that evaluated the pharmacokinetics, efficacy, or safety of Gla-300 were reviewed.

Pharmacokinetics and Pharmacodynamics

Pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of Gla-300 have been studied in various populations with T1DM. All studies used euglycemic glucose clamp technique, the gold standard for measuring PK/PD properties of new insulin formulations. In clamp studies, insulin is injected, followed by a continuous glucose infusion to maintain a prespecified blood glucose level, typically euglycemia. Glucose infusion rates, blood glucose, and plasma insulin levels are measured to assess PK and PD parameters.²¹

PK and PD profiles of 2 Gla-300 formulations were evaluated in a double-blind, randomized, crossover study. Fifty subjects with T1DM (38 males, 12 females; mean age 42.1 years; mean body mass index [BMI] 25.4 kg/m²) received 0.4 units/kg once daily of Gla-300 in a standard insulin pen cartridge formulation in one treatment arm or in a vial with polysorbate-20 (added to enhance stability) in the other treatment arm. Insulin was administered for 6 days followed by a 24-hour euglycemic clamp evaluation. Both formulations of Gla-300 resulted in flat, evenly distributed activity over 24 hours with an extended terminal half-life (INS- $t_{1/2}$) of 17 to 19 hours. Steady-state concentrations were achieved after 3 to 4 days. Gla-300 appears to have a more gradual and extended release from the subcutaneous depot after administration compared to the Gla-100 INS- $t_{1/2}$ of 12 hours and time to steady-state of 2 days. The results of this study indicate bioequivalence of the Gla-300 pen cartridge and vial formulations.²²

Another study evaluated PK and PD characteristics of Gla-300 at 2 different doses compared to Gla-100 in a randomized, double-blind, parallel, crossover study of 30 adults aged 18 to 65 years with T1DM. Baseline characteristics of the Gla-300 0.4 units/kg/day cohort (cohort 1) included 1 female and 17 male subjects, mean age of 44.9 years, an average T1DM duration of 26.9 years, mean BMI of 25.9 kg/m², and mean HbA_{1c} of 7.8%. Baseline characteristics of the Gla-300 0.6 units/kg/day cohort (cohort 2) included 1 female and 11 male subjects, mean age of 41 years, average T1DM duration of 26.5 years, mean BMI of 24.8 kg/m², and mean HbA_{1c} of 8.0%. Participants received the study medication (Gla-300 0.4 units/kg/day or Gla-300

0.6 units/kg/day) in the first treatment period and the control medication (Gla-100 0.4 units/kg/day) in the second period, or vice versa depending on the randomization sequence. Each medication was administered for 8 days, followed by application of a 36-hour euglycemic clamp. The washout period between treatment periods was 5 to 19 days.¹⁸ Multiple doses of Gla-300 at steady state produced similar findings as a previous single-dose study.²³ Serum insulin concentration (INS) and glucose infusion rate (GIR) with Gla-300 were more gradual and evenly distributed in a dose-dependent manner than with the standard dose of Gla-100. In cohort 1, duration of Gla-300 activity extended beyond 24 hours as demonstrated by a 2.49 hour (95% confidence interval [CI] 1.05 to 4.77) difference in time to 50% of the area under the INS and GIR curve ($T_{50\%}$ -GIR-AUC₀₋₃₆). Strict glycemic control (≤ 105 mg/dL) with Gla-300 was maintained for 4.7 hours longer (median 29.5 hours) in cohort 1 and for 6.7 hours longer (median 32.3 hours) in cohort 2, as compared to Gla-100.¹⁸

Two similar single-dose, multi-arm, double-blind, randomized, crossover studies were conducted in Japan and Europe. Japanese participants with T1DM ($n = 18$; 16 males, 2 females; mean age 34.8 years; mean BMI 22.42 kg/m²) were randomized to 3 treatments, Gla-300 0.4 units/kg, 0.6 units/kg, or Gla-100 0.4 units/kg. European participants with T1DM ($n = 24$; 19 males, 5 females; mean age 42.6 years; mean BMI 25.6 kg/m²) were randomized to 4 treatments, Gla-300 0.4 units/kg, 0.6 units/kg, 0.9 units/kg, or Gla-100 0.4 units/kg. Median concentrations of Gla-300 0.6 units/kg were detectable at 32 hours postdose and up to 36 hours in the 0.9 units/kg arm of the European cohort. The Japanese cohort taking Gla-300 0.6 units/kg had detectable insulin concentrations at 36 hours postdose. Glycemic control was maintained up to 36 hours with all doses of Gla-300. Maximum glucose concentration and exposure over 24 hours after an insulin glargine injection were more pronounced with Gla-100 than any dose of Gla-300, providing further evidence that Gla-300 has a flatter and more stable PK profile compared to Gla-100.²⁴

Clinical Efficacy and Safety

At the time of this writing, 6 open-label clinical trials have been completed comparing the efficacy and safety of U-300 to U-100 insulin glargine. Four clinical trials have been conducted in participants with T2DM. Three were multinational, multicenter studies and one was a multicenter study of Japanese subjects.²⁵⁻²⁸ Two clinical trials have been conducted in participants with T1DM. One was a multinational, multicenter study and the other was a multicenter study of Japanese subjects.^{29,30} A summary of published Gla-300 Phase III clinical trials is provided in Table 2.

Insulin Glargine U300 in Type 2 Diabetes

EDITION 1 Trial. The first study in the Phase III EDITION program compared the safety and efficacy of Gla-300 to Gla-100 in 807 participants with T2DM (mean age 60 years, average duration of diabetes 16 years, mean BMI 36.6 kg/m², mean HbA_{1c} 8.15%, mean fasting plasma glucose [FPG] 160 mg/dL) that were also using mealtime insulin. The EDITION 1 study was a 6-month, multicenter, randomized controlled, parallel-group, noninferiority trial. The inclusion criteria consisted of age ≥ 18 years with a diagnosis of T2DM; use of ≥ 42 units per day of Gla-100 or NPH insulin and either insulin aspart, lispro, or glulisine, with or without metformin for at least 1 year; and HbA_{1c} of 7.0% to 10.0%. Exclusion criteria included use of premixed insulin or basal insulin other than Gla-100 or NPH, OADs other than metformin within the past 3 months, or noninsulin injectable glucose-lowering medications; a history of proliferative diabetic or unstable retinopathy; or significant systemic diseases such as cardiac, renal, or hepatic disease.²⁵

Participants were randomized in a 1:1 ratio to receive Gla-300 ($n = 404$) or Gla-100 ($n = 403$) and were stratified based on HbA_{1c} of < 8.0 or $\geq 8.0\%$. Upon stratification, participants administered insulin in the evening at a starting dose equal to the total basal dose used during the 3 days prior to randomization if they were previously using Gla-100 or once daily NPH. If the participant was previously on twice daily NPH, the study dose was equal to 80% of the total daily dose. Weekly insulin glargine dose adjustments were based on the protocol outlined in Table 3. Mealtime insulin doses could be decreased if needed; however, dose increases occurred once basal insulin was optimized.²⁵

After 6 months, there was no difference between groups in the primary endpoint of change in HbA_{1c} (least squares (LS) mean -0.83% , 0.0% difference [95% CI -0.11 to 0.11]). Noninferiority of Gla-300 was proven, as the prespecified mean difference in HbA_{1c} between groups was $< 0.4\%$. Change in FPG was similar between groups (LS mean -23 for Gla-300, -25 for Gla-100). The percentage of patients that attained HbA_{1c} $< 7\%$ and $\leq 6.5\%$ were also similar between groups. Basal insulin dose of Gla-300 increased from 0.67 units/kg/day (70 units/day) to 0.97 units/kg/day (103 units/day) at study end, Gla-100 increased from 0.67 units/kg/day (71 units/day) to 0.88 units/kg/day (94 units/day) (LS mean difference 0.09 units/kg/day [95% CI 0.062 to 0.124]).²⁵

Both treatment groups experienced a 0.9 kg weight gain. Rates of confirmed (blood glucose ≤ 70 mg/dL) or severe (requiring assistance by another individual) nocturnal hypoglycemia between the start of week 9 and month 6 were 36% with Gla-300 and 46% with Gla-100 (relative risk [RR] 0.79 [95% CI 0.67 to 0.93], $P = .0045$). The rate of hypoglycemia at any time was 15% lower in the Gla-300 group from baseline to week 8 (RR 0.85 [95% CI 0.78 to

Table 2. Summary of Randomized Controlled Trials of Insulin Glargine 300 units/mL.

Study	Duration	Design and Population	Treatment Regimen	HbA _{1c} (%) Change From Baseline ^a	FPG (mg/dL) Change From Baseline ^a	Body Weight (kg) Mean Change From Baseline	Hypoglycemia, Any Time of Day ^b RR (95% CI)
Type 2 diabetes studies							
Bolli et al ²⁷ (EDITION 3); N = 878	6 months	Open-label, multinational in insulin-naïve participants	Gla-300 vs Gla-100 SFU were stopped	0.04 (−0.09 to 0.17)	NR	Gla-300: 0.4 (SD 3.8) Gla-100: 0.7 (SD 3.8)	0.88 (0.77 to 1.01)
Riddle et al ²⁵ (EDITION 1); N = 811	6 months	Open-label, multinational	Gla-300 vs Gla-100 Both regimens included mealtime insulin	−0.00 (−0.11 to 0.11)	Gla-300: −1.29 (SD 0.19) Gla-100: −1.38 (SD 0.19)	Increase of 0.9 kg in both groups	0.93 (0.88 to 0.99)
Riddle et al ³¹ (EDITION 1); N = 714	12-month extension	Open-label, multinational	Gla-300 vs Gla-100 Both regimens included mealtime insulin	−0.17 (−0.30 to −0.05)	−6.13 (−12.43 to 0.18)	NR	0.94 (0.89 to 0.99)
Terauchi et al ²⁸ (EDITION JP2); N = 241	6 months	Open-label in Japanese participants	Gla-300 vs Gla-100 Both groups continued OADs	0.10 (−0.08 to 0.27)	NR	Gla-300: −0.62 (SD 0.19) Gla-100: 0.37 (SD 0.19)	0.86 (0.73 to 1.01)
Yki-järvinen et al ²⁶ (EDITION 2); N = 811	6 months	Open-label, multinational	Gla-300 vs Gla-100 Both groups continued OADs, except SFU	−0.01 (−0.14 to 0.12)	3.42 (−2.7 to 9.37)	Gla-300: 0.08 (SD 3.45) Gla-100: 0.66 (SD 3.01) P = .015	0.90 (0.83 to 0.98)
Yki-järvinen et al ³² (EDITION 2); N = 629	12-month extension	Open-label, multinational	Gla-300 vs Gla-100 Both groups continued OADs, except SFU	0.06 (−0.22 to 0.10)	NR	Gla-300: 0.42 (0.04 to 0.80) Gla-100: 1.14 (0.76 to 1.52) P = .0091	0.96 (0.89 to 1.02)
Type 1 diabetes studies							
Home et al ²⁹ (EDITION 4); N = 549	6 months	Open-label, multinational	Gla-300 vs Gla-100 Both regimens included mealtime insulin	0.04 (−0.10 to 0.19)	NR	Gla-300 vs Gla-100 mean difference: −0.56 (−1.09 to 0.03)	1.09 (0.94 to 1.25)
Matsuoka et al ³⁰ (EDITION JP1); N = 243	6 months	Open-label in Japanese participants	Gla-300 vs Gla-100 Both regimens included mealtime insulin	0.13 (−0.03 to 0.28)	NR	NR	0.99 (0.95 to 1.04)

Abbreviations: Gla-300, insulin glargine 300 units/mL; Gla-100, insulin glargine 100 units/mL; NR, not reported; RCT, randomized-controlled trial; OADs, oral antidiabetic drugs; SFU, sulfonylurea; SD, standard deviation; RR, relative risk; FPG, fasting plasma glucose; CI, confidence interval.

^aLeast squares mean difference (95% confidence interval); compared to insulin glargine 100 units/mL, unless otherwise noted.

^bConfirmed (≤70 mg/dL) or severe (requiring assistance by another person).

Table 3. Insulin Glargine 300 Units/mL Dose Adjustment Protocol²⁵⁻²⁷.

Median Blood Glucose Level Over Past 3 Days (mg/dL)	Change in Daily Insulin Dose ^a
<79	Decrease by 3 units ^b
80 to 99	Continue current regimen
100 to 139	Increase by 3 units
≥140	Increase by 6 units

^aInsulin doses were adjusted weekly, no more often than every 3 days.

^bEDITION 3 investigators could decrease doses by more than 3 units if glucose was <59 mg/dL or severe or multiple symptomatic hypoglycemic events occurred. EDITION 1 investigators could decrease doses by 3 units at their discretion.

0.93]). Incidence rates of hypoglycemia at any time from baseline to month 6 and week 9 to month 6 were similar between treatment groups (RR 0.94 [95% CI 0.89 to 1.00]; RR 0.98 [95% CI 0.90 to 1.05], respectively). Rates of nocturnal hypoglycemia were significantly lower in the Gla-300 group (baseline to month 6, RR 0.76 [95% CI 0.66 to 0.87]; baseline to week 8, RR 0.72 [95% CI 0.72 to 0.89]; week 9 to month 6, RR 0.8 [95% CI 0.68 to 0.95]). The frequency and type of adverse events were equally distributed between groups. Serious treatment emergent adverse events were reported by 6.4% of subjects on Gla-300 and 5.2% of subjects on Gla-100. The investigators defined a treatment emergent adverse event (TEAE) as any event not present prior to the initiation of treatments or any event already present that worsened in either intensity or frequency following exposure to the treatments.²⁵

A 6-month extension of the EDITION 1 trial observed that improved glycemic control persisted, although changes in HbA_{1c} and FPG were smaller in the Gla-300 group after the 12-month follow-up compared to the 6-month follow-up. Mean change in HbA_{1c} after 12 months was -0.17% (95% CI -0.30 to -0.05). Mean change in FPG was -6.13 mg/dL (95% CI -12.43 to 0.18). Participants using Gla-300 experienced decreased rates of hypoglycemia compared to Gla-100; however, the difference in nocturnal hypoglycemia was more significant (confirmed or severe hypoglycemia at any time of day RR 0.94 [95% CI 0.89 to 0.99]; nocturnal hypoglycemia RR 0.84 [95% CI 0.75 to 0.94]). Additionally, the Gla-300 group utilized higher basal insulin doses relative to Gla-100 (1.03 units/kg vs 0.90 units/kg).³¹

EDITION 2 Trial. The second study in the EDITION series compared the safety and efficacy of Gla-300 to Gla-100 in 811 participants with T2DM (mean age 58 years, average duration of diabetes 13 years, mean BMI 34.8 kg/m², mean HbA_{1c} 8.24%, mean FPG 145 mg/dL) using OADs with basal insulin. EDITION 2 was a 6-month, multicenter,

open-label, randomized controlled, noninferiority trial. Inclusion criteria consisted of age ≥18 years, a diagnosis of T2DM for at least 1 year, 6 months on basal insulin (≥42 units/day of Gla-100 or NPH) combined with OADs. Exclusion criteria included HbA_{1c} <7% or >10%; use of premixed insulin, insulin detemir, or a new glucose-lowering agent in the past 3 months; use of a sulfonylurea in the past 2 months; use of regular or mealtime insulin >10 days in the past 3 months; rapidly progressing diabetic retinopathy; end-stage renal disease; or clinically significant cardiac, hepatic, or other systemic disease. Insulin glargine was administered every evening and doses were titrated once weekly per the protocol described in Table 3 to a target FPG reading between 70 and 100 mg/dL. Insulin starting doses were not provided by the authors. Dose adjustments were based on the median blood glucose values recorded during the 3 days prior to follow-up with study investigators. Participants were instructed to continue their OADs at the current stable dose.²⁶

At month 6, the LS mean change in HbA_{1c} was -0.57% (standard error [SE] 0.09) for the Gla-300 group and -0.56% (SE 0.09) for the Gla-100 group (LS mean difference -0.01% [SE 0.07, 95% CI -0.14 to 0.12]). Noninferiority of Gla-300 was proven, as the predefined mean difference in HbA_{1c} between groups was <0.4%. The secondary endpoints showed similar safety and efficacy between both treatment groups. The percentage of patients reaching a target HbA_{1c} <7% and ≤6.5% was 30.6% and 14.5%, respectively, with Gla-300 and 30.4% and 14.8% with Gla-100. The mean FPG was 119 mg/dL in the Gla-300 group and 113 mg/dL in the Gla-100 group at month 6. The Gla-300 group required 10% more basal insulin daily. Mean daily basal insulin dose increased from 0.64 to 0.92 units/kg/day (91 units/day) in the Gla-300 arm versus a mean daily basal insulin dose increase from 0.66 to 0.84 units/kg/day (82 units/day) in the Gla-100 arm.²⁶

The average weight gain observed was statistically lower with Gla-300 compared to Gla-100 (0.08 [SD 3.45] kg vs 0.66 [SD 3.01] kg, *P* = .015). Rates of any hypoglycemia at any time were significantly lower in the Gla-300 arm from baseline to month 6 (RR 0.90 [95% CI 0.83 to 0.98]) and from baseline to week 8 (RR 0.77 [95% CI 0.68 to 0.88]). The risk of hypoglycemia at any time from week 9 to month 6 was similar between the 2 study arms (RR 0.91 [95% CI 0.82 to 1.01]). Rates of any nocturnal hypoglycemia were significantly lower in the Gla-300 arm from baseline to month 6 (RR 0.73 [95% CI 0.60 to 0.88]) and from baseline to week 8 (RR 0.54 [95% CI 0.40 to 0.71]). The risk of nocturnal hypoglycemia at any time from week 9 to month 6 was similar between the 2 study arms (RR 0.80 [95% CI 0.63 to 1.00]). Incidences of confirmed (≤70 mg/dL) or severe nocturnal hypoglycemia were significantly lower in the Gla-300 group from baseline to month 6 (RR 0.71 [95% CI 0.58 to 0.86]), baseline to week 8 (RR 0.53 [95% CI 0.39

to 0.72]), and week 9 to month 6 (RR 0.77 [95% CI 0.60 to 0.97]). The incidence of treatment-related adverse events was lower in the Gla-300 group (1.7%) than in the Gla-100 group (3.7%). Incidences of serious TEAE were the same (3.7%) in both study groups.²⁶

A 6-month extension of the EDITION 2 trial showed effects on HbA_{1c} persisted. The rate of confirmed or severe nocturnal hypoglycemic events was 37% lower in the Gla-300 group compared to Gla-100 (RR 0.63 [95% CI 0.42 to 0.96]). Over the 1-year study period, the mean weight gain observed was also lower in the Gla-300 group compared to the Gla-100 group (0.42 kg vs 1.14 kg, $P = .0091$).³²

EDITION 3 Trial. EDITION 3 was a 6-month, multicenter, open-label, 2-arm, parallel-group, randomized study evaluating the safety and efficacy of Gla-300 compared to Gla-100 in 878 insulin-naïve subjects with uncontrolled T2DM (mean age 57.7, average duration of diabetes 9.8 years, mean BMI 33.0 kg/m², mean HbA_{1c} 8.54%). Inclusion criteria consisted of age ≥ 18 years with a diagnosis of T2DM for at least 1 year, treatment with OADs for a minimum of 6 months, and being insulin-naïve.²⁷ Exclusion criteria included the following: HbA_{1c} $< 7\%$ or $> 11\%$, a change in glucose-lowering therapy or initiation of weight-loss medication in the previous 3 months, initiation of glucagon-like peptide-1 (GLP-1) receptor agonist in the previous 6 months, insulin use during the previous year, and rapidly progressive diabetic retinopathy or macular edema requiring treatment during the study.³³ Study participants continued OADs throughout the trial; however, OADs not approved for use in combination with insulin, sulfonylureas, and glinides were discontinued at baseline. Once-daily insulin glargine was administered any time before the evening meal and bedtime at the same time every day. Initiation doses were 0.2 units/kg rounded down to the closest number divisible by 3. Dose adjustments were made once weekly according to the protocol outlined in Table 3 to reach a target FPG of 80 to 100 mg/dL if hypoglycemia was not present. When more than one injection was necessary to deliver a single dose, injections were given at the same time.²⁷

OADs continued throughout the trial were metformin (91%) and dipeptidyl peptidase-4 inhibitors (22%). There were 59% of subjects taking sulfonylureas at baseline and discontinued the medication at study initiation. The LS mean difference in HbA_{1c} of Gla-300 compared to Gla-100 after 6 months was 0.04% (95% CI -0.09 to 0.17). The percentages of subjects reaching a target HbA_{1c} $< 7\%$ and $\leq 6.5\%$ were similar between groups (43.1% and 25%, respectively, with Gla-300; 42.1% and 27.4% with Gla-100). Mean FPG was 120 mg/dL in the Gla-300 group and 113 mg/dL in the Gla-100 group at month 6. The Gla-300 group required higher basal insulin doses. The Gla-300 arm received a mean (SD) dose of 0.62 (0.29) units/kg/day (59.4

[32.3] units/day) and the Gla-100 arm received 0.53 (0.24) units/kg/day (52.0 [27.8] units/day).²⁷

The incidence of any confirmed (glucose ≤ 70 mg/dL) or severe hypoglycemic event was nonsignificantly lower with Gla-300 over 6 months (RR 0.88 [95% CI 0.77 to 1.01]). Risks of confirmed or severe nocturnal hypoglycemia were: baseline to month 6, RR 0.76 (95% CI 0.59 to 0.99); baseline to week 8, RR 0.74 (95% CI 0.48 to 1.13); week 9 to month 6, RR 0.89 (95% CI 0.66 to 1.20). Weight gain was similar in the Gla-300 and Gla-100 groups (LS mean change 0.49 kg [95% CI 0.14 to 0.83] vs 0.71 kg [95% CI 0.36 to 1.06], respectively). There were no differences in the incidence of TEAE between groups, as 6% of subjects in both treatment groups reported such an event.²⁷

EDITION JP2 Trial. EDITION JP2 was a 6-month, multicenter, open-label, randomized study comparing the safety and efficacy of Gla-300 and Gla-100 in addition to OADs in 241 Japanese participants with T2DM (mean age 60.8 years, mean BMI 25.3 kg/m², average duration of diabetes 14 years, mean HbA_{1c} 8.0%).²⁸ Study participants had been diagnosed with T2DM for at least 1 year and were treated with basal insulin in combination with OADs for 6 months prior to study inclusion. Exclusion criteria consisted of the following: age < 18 years, BMI ≥ 35 mg/kg², HbA_{1c} $< 7\%$ or $> 10\%$; use of premix insulin, insulin detemir administered more than once daily, use of a GLP-1 receptor agonist, use of mealtime insulin for ≥ 10 days, or initiation of new anti-hyperglycemic or weight loss medications during the previous 3 months; use of an insulin pump, hypoglycemic events resulting in coma or seizures, or hospitalization for diabetic ketoacidosis in the previous 6 months; and severe retinopathy or macular edema requiring treatment.³⁴ Glargine insulin doses were adjusted to achieve FPG 80 to 100 mg/dL.²⁸

Similar reductions in HbA_{1c} were observed in both groups (LS mean difference 0.10%, 95% CI -0.08 to 0.27). Similar to findings in EDITION 3, the risk of hypoglycemia was not consistently lower with Gla-300 in all cases. The risk of any confirmed (glucose ≤ 70 mg/dL) or severe hypoglycemic event was nonsignificantly lower with Gla-300 over 6 months (RR 0.86 [95% CI 0.73 to 1.01]). Participants experienced a reduction in nocturnal hypoglycemia between baseline and month 6, particularly from week 9 to month 6 (baseline to month 6, RR 0.62 [95% CI 0.44 to 0.88]; baseline to week 8, RR 0.83 [95% CI 0.45 to 1.52]; week 9 to month 6, RR 0.58 [95% CI 0.40 to 0.85]). Small weight loss was observed with Gla-300 (LS mean change -0.62 kg [SE 0.18]) compared to weight gain with Gla-100 (0.37 kg [SE 0.19]). Detailed study methodology including which OADs were combined with the study treatment, starting doses of insulin, and insulin dose adjustment protocol; and results including mean insulin doses and effects on FPG were not reported in the published abstract.²⁸

Insulin Glargine U300 in Type 1 Diabetes

EDITION 4 Trial. EDITION 4 was a 6-month, multinational, multicenter, open-label, randomized study comparing the safety and efficacy of Gla-300 and Gla-100 in 549 adult participants with T1DM (mean BMI 27.6 kg/m², duration of diabetes 21 years, HbA_{1c} 8.12%).²⁹ Exclusion criteria consisted of the following: HbA_{1c} <7% or >10%; <1 year of treatment with basal plus mealtime insulin; unstable insulin doses during the previous 30 days; use of premix insulin, human regular insulin, or glucose-lowering drugs other than basal plus mealtime insulin in the previous 3 months; use of an insulin pump, hypoglycemic events resulting in coma or seizures, or hospitalization for diabetic ketoacidosis in the previous 6 months; and severe retinopathy or macular edema requiring treatment.³⁵ Subjects administered either Gla-300 or Gla-100 in the morning or evening and continued mealtime insulin. The study methodology did not detail the starting doses of insulin or the insulin dose adjustment protocol used.²⁹

Changes in HbA_{1c} from baseline to month 6 were similar between groups (LS mean difference 0.04% [95% CI -0.10 to 0.19]). Higher doses of Gla-300 were required versus Gla-100 (dose change from baseline 0.19 vs 0.10 units/kg). A statistical difference in hypoglycemia was only found with the nocturnal event rate from baseline to week 8 (baseline to month 6, RR 0.90 [95% CI 0.71 to 1.14]; baseline to week 8, RR 0.69 [95% CI 0.53 to 0.91]; week 9 to month 6, RR 1.04 [95% CI 0.80 to 1.36]). No difference between groups was found in the incidence of confirmed (glucose ≤70 mg/dL) or severe hypoglycemic events at any time of day (baseline to month 6, RR 1.09 [95% CI 0.94 to 1.25]). Weight gain was not largely different between groups (mean difference -0.56 [95% CI -1.09 to -0.03]). No differences in efficacy or safety measures were found between the morning and evening injection groups.²⁹

EDITION JP1 Trial. EDITION JP1 was a 6-month, multicenter, open-label, randomized study comparing the safety and efficacy of Gla-300 and Gla-100 in 243 adult Japanese participants with T1DM (mean age 45.2 years, average duration of diabetes 13 years, mean HbA_{1c} 8.1%).³⁰ The exclusion criteria mimicked the criteria used in the EDITION 4 study.³⁶ Each type of glargine insulin was titrated to target FPG levels 80 to 130 mg/dL and mealtime insulin was continued. Comparable changes in HbA_{1c} were observed in both groups (LS mean difference 0.13% [95% CI -0.03 to 0.29]). Similar to findings in the EDITION 4 trial, rates of overall hypoglycemic events were similar between groups (confirmed [≤70 mg/dL] or severe hypoglycemia any time of day RR 0.99 [95% CI 0.95 to 1.04]). A statistical difference in nocturnal hypoglycemia was only observed from baseline to week 8 (baseline to month 6, RR 0.85 [95% CI 0.73 to 0.99]; baseline to week 8, RR 0.71

[95% CI 0.56 to 0.91]; week 9 to month 6, RR 0.84 [95% CI 0.70 to 1.00]). No differences in the occurrence of adverse events were observed. Detailed study methodology including starting doses of insulin and insulin dose adjustment protocol; and results including mean insulin doses, effects on FPG, and weight changes were not reported in the published abstract.³⁰

Conclusion

Efficacy and safety of Gla-300 have been studied in more than 4500 subjects with type 1 and type 2 diabetes. Clinical trial data have demonstrated the potential of Gla-300 to improve glycemic control with similar efficacy and safety as Gla-100. The most commonly reported adverse events in clinical trials were infections, gastrointestinal events, musculoskeletal complaints, and hypoglycemia.²⁵⁻²⁷ Overall, the incidence of hypoglycemia was not notably different between Gla-300 and Gla-100.²⁵⁻³² Rates of nocturnal hypoglycemia with Gla-300 were lowered by 16% to 38% in type 2 diabetes clinical trials; however, this finding approached nonsignificance in some cases.^{25-28,31,32} The US FDA approved Gla-300 in February 2015.¹⁹ The approved package insert does not report a lower incidence of hypoglycemia compared to Gla-100 and states there were no significant differences in hypoglycemia compared to Gla-100 among study participants with T1DM.⁶ In May 2014, the marketing authorization for Gla-300 was accepted by the EMA followed by the EMA Committee for Medicinal Products for Human Use recommending approval of Gla-300 in February 2015.^{20,37} The final approval decision by the EMA is anticipated before summer 2015.³⁸

Gla-300 will only be available in a disposable prefilled pen; therefore, it will not carry the same safety concerns related to dosing and administration errors as U-500 insulin. Higher doses of Gla-300 were required to achieve the same glycemic control as Gla-100 in clinical trials. It was observed that basal insulin needs were 11% to 17.5% more with Gla-300; however, more aggressive fasting glucose levels were targeted in efficacy studies than what is often desired in clinical practice.^{6,25-27} Despite the higher doses of Gla-300 used in clinical trials, weight gain did not significantly differ compared to Gla-100.²⁵⁻³² Patients converting from a once-daily long- or intermediate-acting insulin to Gla-300 can be initiated at the same unit-per-unit dose. When changing from twice daily NPH, initiate Gla-300 at 80% of the total daily NPH dose.⁶ Glucose levels should be monitored closely after initiating Gla-300 and dose adjustments made accordingly to achieve glycemic control.

Limitations of the available clinical trials include an open-label design and short trial duration. Extrapolation of Gla-300 trial results to all ethnic groups is difficult as study participants were predominantly Caucasian or Japanese.²⁵⁻³² Gla-300 has only been studied in participants with moderately

elevated HbA_{1c} at randomization due to exclusion criteria of HbA_{1c} >10% or >11%,²⁵⁻³⁰ resulting in mean baseline values of 8.0% to 8.6%.²⁵⁻³⁰ The flat and gradual release of Gla-300 from the subcutaneous depot has demonstrated a more prolonged time-action profile with glucose lowering effects lasting up to 36 hours.^{18,23,24} It is unknown if this extended-release characteristic will translate into more flexible once-daily dosing, warranting additional studies. There are a number of other populations and clinical scenarios in which Gla-300 has not been studied. Data in the pediatric population, elderly, pregnancy, and in patients with renal or hepatic disease are lacking. A clinical trial investigating the efficacy and safety of Gla-300 compared to Gla-100 in patients ≥65 years old with T2DM is currently underway with expected completion in 2017.³⁹ Additional experience is needed to determine the effects of Gla-300 compared to insulins other than Gla-100, when combined with sulfonylureas or GLP-1 agonists, how to convert from basal insulins other than Gla-100 or NPH, treating patients with very high HbA_{1c}, and the impact on quality of life. Additionally, clinical trial data beyond 12 months and cardiovascular outcome studies with Gla-300 are lacking.

Gla-300 has demonstrated improvement of glycemic control in persons with T1DM and T2DM, offering another long-acting insulin option. Its place in clinical practice remains to be seen and will largely be affected by competitive pricing and negotiated discounts with third-party payers. Gla-300 may be preferred in patients with T2DM who are susceptible to hypoglycemia or require twice-daily administration of other basal insulin formulations.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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