Advances in Insulin Therapy: A Review of New Insulin Glargine 300 Units/mL in the Management of Diabetes

John R. White, Jr.

IN BRIEF New insulin glargine 300 units/mL (Gla-300) is a formulation of insulin glargine that has a more constant pharmacokinetic profile with a prolonged duration of action. The EDITION clinical trial program showed that the use of Gla-300 leads to glycemic control comparable to that of insulin glargine 100 units/mL in a wide range of populations of people with diabetes. It is associated with comparable to less nocturnal confirmed or severe hypoglycemia and less weight gain, despite requiring a somewhat higher insulin dose than U-100. The distinct pharmacokinetic/pharmacodynamic and clinical profiles of Gla-300 may benefit a range of people with type 1 or type 2 diabetes.

The use of long-acting basal insulin analogs has contributed significantly to improvements in diabetes management over the past decade. Their longer duration of action, with a less distinct peak of action compared to NPH insulin, results in improved glycemic control and an associated reduction in hypoglycemia (1–6). The reduction in hypoglycemia seen with the long-acting basal insulins is important both in terms of clinical outcomes and in addressing patients' and clinicians' fears of hypoglycemia, which may affect both willingness to initiate or titrate insulin therapy and patient adherence to treatment (7). The long-term safety of long-acting insulin glargine 100 units/mL (Gla-100) is also well established (8), and this formulation has been shown to have a neutral effect on cardiovascular outcomes and cancer (9,10).

Recently, newer basal insulins have been developed that have an even longer duration of action with less variation in blood glucose control, and with these there has been a trend toward a reduction in nocturnal hypoglycemia. These new basal insulins include insulin degludec (11–13), basal insulin peglispro (14,15), and new insulin glargine 300 units/mL (Gla-300).

Gla-300 is a new formulation of insulin glargine that delivers the same number of insulin units as Gla-100, but in one-third the injection volume. Pharmacokinetic (PK)/pharmacodynamic (PD) studies have shown that, after injection, Gla-300 is released more gradually from the subcutaneous tissue than Gla-100, giving a more constant PK profile with a prolonged duration of action beyond 24 hours (16–18). The less pronounced peak of action could theoretically result in a more gradual reduction in blood glucose, with a reduced risk of hypoglycemia, while achieving glycemic control; however, this would need to be confirmed clinically in phase 3 trials. Gla-300 has undergone phase 3 clinical trial assessment (the EDITION clinical trial program), the results of which are discussed below. Gla-300 was approved in early 2015 by both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency.

Department of Pharmacotherapy, Washington State University, College of Pharmacy, Spokane, WA

Corresponding author: John R. White, Jr., whitej@wsu.edu

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An additional consideration for new insulin formulations is the requirement for larger doses of insulin in some populations, particularly in obese individuals and those with insulin resistance. Increasing the dose of insulin using conventional 100 units/mL solutions of basal insulin is challenging given the limitations of dispensing large volumes from syringes or pens. The need for high-volume injections, with consequent discomfort and possible injection-site adverse events, could potentially reduce adherence in patients requiring large insulin doses (20). In addition, very large volumes of insulin may have different PK properties (21). Gla-300 may help to overcome some of these issues by reducing the volume of injections required, in addition to the possible benefits provided by its distinct PK/PD properties.

This article reviews the new long-acting insulin Gla-300, the results from the EDITION clinical trial program, the populations who may benefit from this new insulin, and practical information on its use.

EDITION Clinical Trial Program

The efficacy and safety of Gla-300 compared to Gla-100 has been investigated in the phase 3 EDITION clinical trial program, which comprised a series of international, multicenter, randomized, open-label, parallel-group, treat-to-target studies conducted in distinct populations of people with type 1 or type 2 diabetes. The primary endpoint in all studies was noninferiority for A1C change from baseline to month 6, and the main secondary endpoint in the trials of people with type 2 diabetes was the percentage of participants with ≥1 nocturnal (midnight–5:59 a.m.) confirmed (blood glucose ≤70 mg/dL) or severe (per the American Diabetes Association definition) hypoglycemic event from week 9 to month 6.

Gla-300 in Type 2 Diabetes

Data from four studies of Gla-300 in people with type 2 diabetes representing a range of clinical populations are currently available and summarized in Table 1 (22–25). These studies include people not reaching glycemic targets on basal plus mealtime insulin (EDITION 1) (22), basal insulin plus oral antidiabetes drugs in both a multinational (EDITION 2) (23) and a Japanese study (EDITION JP 2) (25), and noninsulin therapies (EDITION 3) (24). The type 2 diabetes EDITION trials have shown consistent efficacy results across the full range of populations studied, successfully meeting the primary endpoint with similar reductions in A1C compared to Gla-100 in all studies.

With respect to hypoglycemia, there was a significant reduction in the main secondary outcome (percentage of individuals experiencing ≥1 nocturnal confirmed or severe hypoglycemic event from week 9 to month 6) with Gla-300 compared to Gla-100 in EDITION 1, 2, and JP 2 (although EDITION JP 2 was not powered to identify a difference in hypoglycemic events) (22–25). Over the 6-month study period, the risk of experiencing ≥1 nocturnal confirmed or severe hypoglycemic event was significantly lower with Gla-300 for all four studies. From baseline to week 8, the risk of experiencing ≥1 nocturnal confirmed or severe hypoglycemic event was reduced in EDITION 1 and 2, but comparable for EDITION 3 and JP 2 (22–25). The risk of people experiencing ≥1 confirmed or severe hypoglycemic event at any time of day over the 6-month study period was significantly lower in EDITION 2 and comparable in EDITION 1, 3, and JP 2 (22–25).

At the end of the 6-month studies, the dose of basal insulin was higher with Gla-300 than with Gla-100 in EDITION 1 (0.97 vs. 0.88 units/kg/day; least squares [LS] mean difference 0.09 units/kg/day; 95% CI 0.062–0.124), EDITION 2 (0.92 vs. 0.84 units/kg/day; LS mean difference 11.14 units/day; 95% CI 8.14–14.14), and EDITION 3 (0.62 units/kg/day vs. 0.53 units/kg/day) (22–24). Despite this, there was less weight gain with Gla-300 than with Gla-100 in EDITION 2 (+0.08 vs. +0.66 kg, P = 0.015), and weight loss in EDITION JP 2 (–0.62 vs. +0.37 kg) (23,25). Weight gain in EDITION 1 was similar for people treated with either Gla-100 or Gla-300 (+0.9 kg in both groups) (22), and numerically less with Gla-300 in EDITION 3 (+0.49 vs. +0.71 kg, NS) (24). In EDITION 1, 2, and 3, treatment satisfaction (measured using the Diabetes Treatment Satisfaction Questionnaire) increased over the 6-month study period to a similar extent for both groups (22–24).

Six-month open-label extension studies of EDITION 1 and 2 resulted in consistent improvements in glycemic control for people treated with both Gla-300 and Gla-100 (28,29). Use of Gla-300 was associated with a significant reduction in the relative risk (RR) of nocturnal confirmed or severe hypoglycemia over the 12-month course of both extension studies (Gla-300 vs. Gla-100, respectively: for EDITION 1, 54.5 vs. 64.7%, RR 0.84 [95% CI 0.75–0.94] and for EDITION 2, 37.5 vs 44.6%, RR 0.84 [95% CI 0.71–0.99]) (28,29). In EDITION 1, the average insulin dose remained ~10% higher with Gla-300 than with Gla-100 after 12 months (1.03 vs. 0.90 units/kg/day) (28). Both groups showed a small increase in body weight in EDITION 2, but this increase was significantly lower with Gla-300 (LS mean difference 0.42 kg [95% CI 0.04–0.80] vs. 1.14 kg [95% CI 0.76–1.52], P = 0.0091) (29).

A substudy of participants in EDITION 1 and EDITION 2 continuing treatment after the initial 6-month trial period compared flexible (allowing between-injection intervals of 24 ± 3 hours on at least 2 days/week) and fixed (once daily in the evening at fixed 24-hour intervals) dosing regimens with Gla-300 over 3 months (30). Change in A1C from baseline was comparable with both the flexible and fixed regimens

TABLE 1. Characteristics, Efficacy, and Safety Endpoints of the EDITION Trials

Study (Ref.)	Population	*n*	Characteristics, Mean	A1C Change:* Baseline to Month 6		Confirmed or Severe Hypoglycemia:† Nocturnal Baseline to Week 8		Nocturnal Week 9 to Month 8		Nocturnal Baseline to Month 6		Any Time of Day Baseline to Month 6		Severe Hypoglycemia:† Baseline to Month 6	
				Gla-300	Gla-100	Gla-300	Gla-100	Gla-300	Gla-100	Gla-300	Gla-100	Gla-300	Gla-100	Gla-300	Gla-100
Type 2 Diabetes															
EDITION 1 (22)	Basal + mealtime insulin	807	Diabetes duration: 16 years BMI: 36.6 kg/m^2 A1C: 8.2%	−0.83%	−0.83% LS mean difference: −0.00% (95% CI −0.11 to 0.11)	26.2%	33.3% RR 0.79 (95% CI 0.64–0.98)	36.1%	46.0% RR 0.79 (95% CI 0.67–0.93)	44.6%	57.5% RR 0.78 (95% CI 0.68–0.89)	81.9%	87.8% RR 0.93 (95% CI 0.88–0.99)	5.0%	5.7% RR 0.80 (95% CI 0.48–1.55)
EDITION 2 (23)	Basal insulin + OADs	811	Diabetes duration: 13 years BMI: 34.8 kg/m^2 A1C: 8.2%	−0.57%	−0.56% LS mean difference: −0.01% (95% CI −0.14 to 0.12)	13.2%	24.6% RR 0.53 (95% CI 0.39–0.72)	21.6%	27.9% RR 0.77 (95% CI 0.60–0.97)	28.3%	39.9% RR 0.71 (95% CI 0.58–0.86)	70.0%	77.3% RR 0.90 (95% CI 0.83–0.98)	1.0%	1.5% NA
EDITION 3 (24)	Insulin naive	878	Diabetes duration: 10 years BMI: 33.0 kg/m^2 A1C: 8.5%	−1.42%	−1.46% LS mean difference: 0.04% (95% CI −0.09 to 0.17)	7.4%	1.0% RR 0.74 (95% CI 0.48–1.13)	15.4%	17.1% RR 0.89 (95% CI 0.66–1.20)	17.9%	23.5% RR 0.76 (95% CI 0.59–0.99)	46.2%	52.5% RR 0.88 (95% CI 0.77–1.01)	0.9%	0.9% NA
EDITION JP 2 (25)	Japanese study; basal insulin + OADs	241	Diabetes duration: 14 years BMI: 25.3 kg/m^2 A1C: 8.0%	−0.45%	−0.55% LS mean difference: 0.10% (95% CI −0.08 to 0.27)	13.3%	16.7% RR 0.83 (95% CI 0.45–1.52)	25.4%	43.7% RR 0.58 (95% CI 0.40–0.85)	28.3%	45.8% RR 0.62 (95% CI 0.44–0.88)	65.0%	76.7% RR 0.86 (95% CI 0.73–1.01)	Infrequent	Infrequent NA
Type 1 Diabetes															
EDITION 4 (26)	Basal + mealtime insulin	549	Diabetes duration: 21 years BMI: 27.6 kg/m^2 A1C: 8.1%	−0.40%	−0.44% LS mean difference: 0.04% (95% CI −0.10 to 0.19)	NA	NA NA	NA	NA NA	NA	NA NA	NA	NA NA	6.6%	9.5% NA

TABLE CONTINUED ON P. 89 →

TABLE 1. Characteristics, Efficacy, and Safety Endpoints of the EDITION Trials *continued from p. 88*

Study (Ref.)	Population	*n*	Characteristics, Mean	A1C Change:* Baseline to Month 6		Confirmed or Severe Hypoglycemia:† Nocturnal Baseline to Week 8		Nocturnal Week 9 to Month 8		Nocturnal Baseline to Month 6		Any Time of Day Baseline to Month 6		Severe Hypoglycemia:† Baseline to Month 6	
				Gla-300	Gla-100	Gla-300	Gla-100	Gla-300	Gla-100	Gla-300	Gla-100	Gla-300	Gla-100	Gla-300	Gla-100
Type 1 Diabetes *continued from p. 88*															
EDITION JP 1 (27)	Japanese study; basal + mealtime insulin	243	Diabetes duration: 13 years A1C: 8.1%	−0.30%	−0.43%	43.4%	61.2%	61.7%	73.7%	−0.00%	−0.00%	−0.00%	−0.00%	Infrequent	Infrequent
				LS mean difference: 0.13% (95% CI −0.03 to 0.29)		RR 0.71 (95% CI 0.56–0.91)		RR 0.84 (95% CI 0.70–1.00)		LS mean difference: −0.00% (95% CI −0 to 0		LS mean difference: −0.00% (95% CI −0 to 0		NA	

**LS mean change. †People experiencing ≥1 hypoglycemic event (safety population). NA, not available; OADs, oral antidiabetes drugs.*

(for EDITION 1, LS mean difference 0.05% [95% CI −0.19 to 0.30] and for EDITION 2, LS mean difference 0.13% [95% CI −0.15 to 0.42]). Similar proportions of participants on each regimen experienced ≥1 nocturnal confirmed or severe hypoglycemic events (flexible vs. fixed, respectively: for EDITION 1, 15 vs. 12% and for EDITION 2, 7 vs. 10%), or ≥1 confirmed or severe hypoglycemic event at any time of day (flexible vs. fixed: for EDITION 1, 32 vs. 35% and for EDITION 2, 16 vs. 18%) (30). These data suggest that flexibility in the timing of daily Gla-300 injections by ±3 hours results in similar efficacy and safety compared to fixed dosing.

In a patient-level meta-analysis of EDITION 1, 2, and 3 (n = 2,496), a similar change in A1C from baseline to month 6 for Gla-300 and Gla-100 was demonstrated (LS mean change −1.02% for both treatments) (31). There was also a reduction in the proportion of people experiencing ≥1 nocturnal confirmed or severe hypoglycemic event (RR 0.75, 95% CI 0.68–0.83) and ≥1 confirmed or severe hypoglycemic event at any time of day (RR 0.91, 95% CI 0.87–0.96) over the 6-month study period (31). There was a small weight gain with both Gla-300 and Gla-100 (+0.49 vs. +0.75 kg) (31).

Gla-300 in Type 1 Diabetes

Data are currently available from two studies of Gla-300 in people with type 1 diabetes not reaching glycemic targets on basal plus mealtime insulin (EDITION 4 and EDITION JP 1) and are summarized in Table 1 (26,27).

As in type 2 diabetes, treatment with Gla-300 and Gla-100 in EDITION 4 led to a similar reduction in A1C over the 6-month study period. Event rates of nocturnal and anytime confirmed or severe hypoglycemia were similar for Ga-300 and Gla-100 over the 6-month study period; there was a reduced rate of nocturnal confirmed or severe hypoglycemia from baseline to week 8 (rate ratio 0.69 [95% CI 0.53–0.91]) (26). Total insulin dose in EDITION 4 was slightly higher for Gla-300 than for Gla-100 (change from baseline +0.19 vs. +0.10 units/kg). Despite this, weight gain was significantly lower with Gla-300 (LS mean difference −0.56 kg; P = 0.037) (26).

In EDITION JP 1, there was also a similar reduction in A1C between Gla-300 and Gla-100 over the 6-month study. Although the study was not powered to assess differences in hypoglycemia, the proportion of subjects experiencing ≥1 nocturnal confirmed or severe hypoglycemic event over the 6-month study, as well as in the first 8 weeks, was significantly lower with Gla-300 (27). A similar proportion of subjects experienced confirmed or severe hypoglycemia at any time of day over the 6-month study (27).

Safety of Gla-300

Clinical trials of Gla-300 have not highlighted any unique adverse event issues arising from the use of this new formulation. The safety profiles of Gla-300 and Gla-100 were similar across all of the EDITION trials (22–29). There was no evidence of increased injection site reactions for Gla-300 compared to Gla-100 in EDITION 1 (2.2 vs 1.5%, respectively), EDITION 2 (0.7 vs. 2.7%), or EDITION 3 (4 vs. 5%) (22–24).

Several safety concerns were previously raised with the use of concentrated insulin following the use of recombinant human regular insulin 500 units/mL (U500). These were largely related to the risk of dosing errors due to confusion between the 500-units/mL and 100-units/mL formulations. Such errors have resulted in incidences of hypoglycemia and hyperglycemia, which have been fatal in rare cases (20). These dosing errors are likely related to the fact that U500 is not available with a calibrated syringe or a pen device and so requires special instructions on its use. The availability of Gla-300 in a pen device that delivers the insulin dose

in standard units of insulin should allay some of the concerns regarding the potential for dosing errors. This may also reduce any confusion in switching between 100-units/mL and 300-units/mL formulations.

Gla-300: Potential Benefits and Practical Tips

A range of people with either type 1 or type 2 diabetes may benefit from treatment with insulins offering a longer activity profile and lower hypoglycemia risk. People at high risk of hypoglycemia or hypoglycemia-related adverse events such as falls are likely to benefit significantly. Those who currently require twice-daily dosing may also benefit from an insulin with a prolonged duration of action, which may allow for once-daily dosing. The possibility for some flexibility in the timing of Gla-300 dosing may benefit people with adherence issues related to rigid dosing schedules or complex regimens (32,33).

People requiring large insulin doses because of severe insulin resistance or obesity are likely to benefit further from the use of Gla-300. "Severe insulin resistance" has been defined as a total daily insulin requirement of ≥200 units or insulin doses >2 units/kg/day (34). The need for large daily insulin doses is associated with large injection volumes and consequent injection site pain (34), with higher numbers of daily injections and increased injection site pain being significant risk factors for nonadherence (35). Gla-300 could provide a reduced dose volume for people who need larger insulin doses. A patient using the Gla-300 pen will be able to administer 80 units in a single injection.

There are some additional practical considerations related to Gla-300 use. Data from the titration phase (the first 8 weeks of treatment) of the EDITION 1 and 2 studies showed reduced risk for nocturnal hypoglycemia (22–24). This may allow for greater confidence in titrating the insulin dose by reducing the fear of nocturnal hypoglycemia. The potential for slightly higher doses with Gla-300 compared to Gla-100 may also need to be considered; people who switch back to their previous therapy may then have a different dose requirement.

Summary and Conclusion

Gla-300 is a new formulation of insulin glargine that has a more constant and prolonged PK profile than Gla-100. The EDITION clinical trial program showed that the use of Gla-300 leads to noninferior glycemic control compared to Gla-100 in a range of populations of people with type 1 or type 2 diabetes. There was also evidence from individual trials for less nocturnal and anytime confirmed or severe hypoglycemia and less weight gain despite a slightly higher insulin requirement. A patient-level meta-analysis of the EDITION trials in people with type 2 diabetes suggests a reduction in confirmed or severe hypoglycemia both nocturnally and at any time of day in the population as a whole.

The clinical profile of Gla-300 may benefit a range of people with either type 1 or type 2 diabetes, particularly those for whom a reduction in the incidence of hypoglycemia would be advantageous. In addition, the use of Gla-300 may also benefit people requiring large doses of insulin by reducing the volume of insulin injections. The use of an insulin pen device will allow for ease of switching to Gla-300 and use of Gla-300 without the need for special instructions.

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Duality of Interest

Dr. White served on an advisory board for Sanofi US.

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