Advances in Basal Insulin Therapy

Jennifer Goldman, PharmD, CDE, BC-ADM, FCCP¹,
and John R. White Jr, PA-C, PharmD²

Abstract

Objective: To review 2 new basal insulin analogs that have been approved in the United States for use in type 1 and type 2 diabetes—insulin glargine 300 units/mL and insulin degludec 100 units/mL and 200 units/mL. **Data Sources:** PubMed was searched using the terms “insulin glargine 300 units/mL,” “Gla-300,” “insulin degludec,” “IDeg,” “insulin degludec 200 units/mL,” and “insulin degludec 100 units/mL” for articles published between 1995 and May 2016. **Study Selection and Data Extraction:** Clinical trials, meta-analyses and subanalyses were identified; review articles were excluded. Relevant citations from identified articles were also reviewed. **Data Synthesis:** The new basal insulins, insulin glargine 300 units/mL and insulin degludec 100 units/mL and 200 units/mL, have improved pharmacokinetic and pharmacodynamic profiles compared to insulin glargine 100 units/mL. All demonstrate longer durations of action, beyond 24 hours, and less variability. These improved profiles translate into comparable A1C reductions and comparable, or improved, levels of hypoglycemia compared to insulin glargine 100 units/mL. **Conclusions:** These benefits may lead to improved glycemic control in a range of patients with type 1 and type 2 diabetes with true once-daily dosing.

Keywords

insulin glargine 300 units/mL, insulin degludec, basal insulin

Introduction

Endogenous insulin secretion is characterized by basal secretion of insulin that maintains normal blood glucose levels throughout the day and night, augmented by pulses of insulin secretion at mealtimes that control postprandial increases in blood glucose level.¹ Insulin treatment for type 1 diabetes (T1D) must provide both types of insulin action (basal and prandial action), while type 2 diabetes (T2D) can often be managed initially with a basal insulin alone. Optimally, the regimen should be tailored to minimize hyperglycemia while avoiding hypoglycemia, and a variety of insulin analogs have been developed for clinical use with this goal in mind. An insulin dose regimen tailored to the individual patient is required to achieve a clinically effective balance of good glycemic control and a low risk of hypoglycemia.

To achieve an appropriate insulin regimen, it is important to consider the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of the insulin products. A basal insulin should provide consistent blood glucose control over a 24-hour period with as little day-to-day variability in blood-glucose-lowering response as possible to allow patients predictable control of their blood glucose.^{2,3} In PK/PD terms, this can be achieved with a basal insulin that has a longer half-life, a flat “peakless” glucose-lowering action, and low within-patient day-to-day variability in glucose-lowering effect. The PK/PD profile of NPH insulin is characterized by a relatively short duration of action, a distinct

peak effect at 4 to 5 hours, and significant interindividual variability in glucose-lowering action.⁴ In contrast, basal insulin analogs such as insulin detemir and insulin glargine 100 units/mL (Gla-100) have improved PK/PD profiles compared to NPH insulin with longer half-lives, flatter activity profiles, and less within-patient variability in dose response.^{5,6} Clinically, these effects translate into easier dose titration, more consistent glycemic control, and a reduced risk of hypoglycemia, with delivery via once- or twice-daily subcutaneous injection.^{7,8} Both Gla-100 and insulin detemir are widely used in current clinical practice. We describe here the newest basal insulin analogs: insulin glargine 300 units/mL (Gla-300) and insulin degludec 100 units/mL and 200 units/mL.

Data Sources

PubMed was searched using the phrases “insulin glargine 300 units/mL,” “Gla-300,” “insulin degludec,” “IDeg,” “insulin degludec 200 units/mL,” and “insulin degludec 100 units/mL.” Dates were limited to between 1995 and May 2016.

¹MCPHS University, Boston, MA, USA

²Washington State University, Spokane, WA, USA

Corresponding Author:

Jennifer Goldman, Pharmacy Practice, MCPHS University, 179 Longwood Ave, Boston, MA 02115, USA.

Email: jennifer.goldman@mcphs.edu

Clinical trials, meta-analyses, and subanalyses were manually identified for inclusion, and review articles were excluded. Relevant citations from identified articles were also reviewed. Abstracts from the American Diabetes Association Scientific Sessions and the European Association of the Study of Diabetes Annual meeting in 2015 were also searched to identify any additional trial data.

Novel Basal Insulins

Gla-300

Gla-300 is a novel formulation of insulin glargine delivering the same amount of insulin glargine as Gla-100 but in one third the volume. It was approved for use in the United States in February 2015. The specific change in concentration of insulin glargine in the Gla-300 formulation is associated with modified absorption kinetics. It is hypothesized that the pH-dependent redissolution of the insulin glargine precipitate is dependent on the size and, therefore, the surface area, of the depot^{9,10}; PK/PD studies of Gla-300 at steady state have shown that this translates to a flatter, more consistent glucose-lowering effect across the 24-hour dose interval and a longer duration of action compared with Gla-100 (Figure 1) that extends the period of blood glucose control beyond 24 hours.^{9,10} With a terminal half-life of approximately 19 hours, the estimated time to reach steady state is 3 to 4 days.¹¹ Gla-300 has also been reported to have a high level of between-day reproducibility and low within-day variability.¹¹ The active metabolite of Gla-300, known as M1, has been shown to be identical to the active metabolite of Gla-100.¹⁴ Given its PK/PD characteristics, Gla-300 provides an attractive profile for a basal insulin. The flat glucose-lowering effect and low within-individual variability offers a predictable response, and the extended duration of action of more than 24 hours allows once-daily dosing.

The Gla-100 formulation of insulin glargine has been used by a large number of people over the past decade, and it is established as an effective and safe basal insulin with a low rate of adverse events and no increase in cardiovascular and cancer risks.¹⁵ Gla-300 was approved on the basis of the results of its comparison with Gla-100 in the EDITION clinical trial program in patients with T2D (EDITION 1, 2, and 3) and T1D (EDITION 4) (Table 1), with 2 additional dedicated Japanese trials.¹⁶⁻²⁰ In the EDITION trials, the primary endpoint was glycated hemoglobin A1c (A1C) change from baseline to month 6 with a noninferiority margin of 0.4%. Hypoglycemia was described as “confirmed” if the blood glucose was ≤ 70 mg/dL and “severe” if assistance was required from another person to actively administer treatment, as defined by the American Diabetes Association.²¹ The nocturnal period was 00:00 to 05:59. In EDITION 1, 2, and 3, the main secondary end point was the percentage of patient experiencing ≥ 1 confirmed or severe nocturnal hypoglycemia event from week 9 to month 6.

EDITION 1 was conducted in patients with T2D who were using basal and mealtime insulin.¹⁶ During the 6 months of the study there was a comparable decrease in A1C with both Gla-300 and Gla-100, and the incidence of confirmed or severe nocturnal or any time of day hypoglycemia events was lower with Gla-300 than Gla-100 (Table 1).¹⁶ The incidence of confirmed or severe nocturnal events between baseline and Week 8 was also lower with Gla-300 (relative risk [RR] 0.79, 95% confidence interval [CI] 0.64-0.98).¹⁶ By the end of the 6-month study, increase in weight in the 2 groups was comparable, and basal insulin doses had slightly increased in both groups with patients in the Gla-300 group needing a dose approximately 10% greater than those in the Gla-100 group (Table 1).¹⁶ In a 6-month extension of EDITION 1, improved glycemic control was maintained over 12 months for both Gla-300 and Gla-100, with a slightly greater A1C decrease with Gla-300 at 12 months (least squares mean difference Gla-300 vs Gla-100: -0.17% [95% CI -0.30 to -0.05]). A significantly smaller percentage of patients experienced ≥ 1 confirmed or severe nocturnal hypoglycemia event (RR 0.84 [95% CI 0.75-0.94]) or an event at any time of day (RR 0.94 [95% CI 0.89-0.99]).²²

The EDITION 2 trial compared Gla-300 with Gla-100 in patients with T2D who were using basal insulin and oral antidiabetes drugs (OADs).¹⁷ During the 6-month trial period, Gla-300 and Gla-100 resulted in comparable improvements in glycemic control, and the incidence of confirmed or severe nocturnal hypoglycemia or hypoglycemia at any time of day was significantly lower with Gla-300 than with Gla-100 (Table 1).¹⁷ Gla-300 also resulted in fewer confirmed or severe nocturnal hypoglycemia events between baseline and Week 8 (RR 0.53 [95% CI 0.39-0.72]).¹⁷ At the end of the 6-month study, patients had gained significantly less weight with Gla-300 than with Gla-100, and insulin dose had increased for both groups (an approximately 10% higher basal insulin dose was observed with Gla-300 than with Gla-100; Table 1).¹⁷ In a 6-month extension of the EDITION 2 trial, glycemic control was maintained with both Gla-300 and Gla-100, and after 12 months a significantly lower percentage of patients using Gla-300 had experienced ≥ 1 confirmed or severe nocturnal hypoglycemia event (RR 0.84 [95% CI 0.71-0.99]) but not at any time of day (RR 0.96 [95% CI 0.89-1.02]).²³

The EDITION 3 trial was conducted in insulin-naïve patients with T2D who were using noninsulin therapies.¹⁸ During the 6-month trial period, comparable improvement in glycemic control was observed with Gla-300 and Gla-100, but the incidence of confirmed or severe nocturnal hypoglycemia was significantly lower with Gla-300 than with Gla-100 (Table 1).¹⁸ The incidence of confirmed or severe hypoglycemia at any time of day was comparable between the groups (Table 1), and there were similar incidences of confirmed or severe nocturnal events from baseline to Week 8 (RR 0.74 [95% CI 0.48-1.13]).¹⁸ At the end

Figure 1. Pharmacokinetic and pharmacodynamic curves for Gla-300 (dose 0.4 U/kg in patients with T1D) (A) insulin concentration curves and (B) glucose infusion rates; and Deg-100 (dose 0.4 U/kg in patients with T1D) (C) insulin concentration curves and (D) glucose infusion AUC values.

Abbreviations: GIR, glucose infusion rate; AUC, area under the curve; INS, insulin; CV, coefficient of variance.

(A and B) Reproduced from Becker et al.¹¹ © 2015 by the American Diabetes Association. (C and D) Reproduced from Heise et al.¹³ © 2015 Taylor & Francis; data from Korsatko et al.¹²

of the 6-month study, observed weight gain was lower with Gla-300 than with Gla-100, and insulin dose was 17% higher with Gla-300 than with Gla-100 (Table 1).¹⁸

The EDITION 4 trial compared the efficacy and safety of Gla-300 and Gla-100 in patients with T1D randomized 1:1 to morning or evening dosing.¹⁹ During the 6-month trial period

overall, Gla-300 provided glycemic control comparable to that obtained with Gla-100; the 2 groups had comparable incidences of confirmed or severe nocturnal hypoglycemia or hypoglycemia at any time of day (Table 1), but incidences of confirmed or severe nocturnal hypoglycemia events between baseline and Week 8 were lower with Gla-300 than with

Table 1. Phase 3 Clinical Trial Results for Insulin Glargine 300 Units/mL

Study	EDITION 1 ¹⁶			EDITION 2 ¹⁷			EDITION 3 ¹⁸			EDITION 4 ¹⁹			Fixed Versus Flexible Dosing ²⁰		
Population	T2D; basal + mealtime insulin			T2D; basal insulin + OADs			T2D; insulin naive			T1D			T2D (EDITION 1 and 2)		
Duration	6 months			6 months			6 months			6 months			3 months		
Treatment	Gla-300	Gla-100		Gla-300	Gla-100		Gla-300	Gla-100		Gla-300	Gla-100		Gla-300 fixed	Gla-300 flexible	
n	404	400		403	405		435	438		274	275		95	99	
A1c reduction, %	-0.83	-0.83		-0.57	-0.56		-1.42	-1.46		-0.42	-0.44		0.00	0.05	
	LS mean difference: -0.00			LS mean difference: -0.01			LS mean difference: 0.04			LS mean difference: 0.04			LS mean difference: 0.05		
	(-0.11 to 0.11)			(-0.14 to 0.12)			(-0.09 to 0.17)			(-0.10 to 0.19)			(-0.13 to 0.23)		
FPG reduction	-1.48 mmol/L	-1.69 mmol/L		-1.14 mmol/L	-1.06 mmol/L		-3.41 mmol/L	-3.80 mmol/L		-17.1 mg/dL	-20.5 mg/dL		3.9 mg/dL	6.6 mg/dL	
	LS mean difference: 0.19			LS mean difference: 0.19			LS mean difference: 0.39			LS mean difference: 2.7			LS mean difference: 2.7		
	(-0.15 to 0.52)			(-0.15 to 0.52)			(0.10 to 0.68)			(-9.0 to 14.4)			(-9.0 to 14.4)		
Nocturnal hypoglycemia	Confirmed (≤ 70 mg/dL) or severe (00:00 to 05:59)			Confirmed (≤ 70 mg/dL) or severe (00:00 to 05:59)			Confirmed (≤ 70 mg/dL) or severe (00:00 to 05:59)			Confirmed (≤ 70 mg/dL) or severe (00:00 to 05:59)			Confirmed (≤ 70 mg/dL) or severe (00:00 to 05:59)		
Baseline-end of study, percentage patients experiencing ≥ 1 event	44.6	57.5		28.3	39.9		17.9	23.5		68.6	70.2		23	21	
Relative risk (95% CI)	0.78 (0.68 to 0.89)			0.71 (0.58 to 0.86)			0.76 (0.59 to 0.99)			0.98 (0.88 to 1.09)			0.94 (0.54 to 1.55)		
Hypoglycemia at any time of day	Confirmed (≤ 70 mg/dL) or severe			Confirmed (≤ 70 mg/dL) or severe			Confirmed (≤ 70 mg/dL) or severe			Confirmed (≤ 70 mg/dL) or severe			Confirmed (≤ 70 mg/dL) or severe		
Baseline-end of study, percentage patients experiencing ≥ 1 event	81.9	87.8		70.0	77.3		46.2	52.5		93.1	93.5		55	47	
Relative risk (95% CI)	0.93 (0.88 to 0.99)			0.90 (0.83 to 0.98)			0.88 (0.77 to 1.01)			1.00 (0.95 to 1.04)			0.85 (0.65 to 1.11)		
Weight change, kg, mean	+0.9	+0.9		+0.08	+0.66		+0.49	+0.71		+0.5	+1.0				
	P = .015			P = .015			P = NS			P = .037					
Basal insulin dose at end of study, mean units/kg/day (SD)	0.97 (0.37)	0.88 (0.32)		0.92 (0.31)	0.84 (0.28)		0.62 (0.29)	0.53 (0.24)		0.47 (0.22)	0.40 (0.18)				
	LS mean difference: 0.09 U/kg/day			LS mean difference: 11.14 U/day			LS mean difference: 11.14 U/day			LS mean difference: 11.14 U/day					
	(0.062 to 0.124)			(8.14 to 14.14)			(8.14 to 14.14)								

Abbreviations: CI, confidence interval; FPG, fasting plasma glucose; LS, least squares; n, number of patients; NS, not significant; OAD, oral antidiabetes drug; SD, standard deviation; T1D, type 1 diabetes; T2D, type 2 diabetes.

Gla-100 (RR 0.82 [95% CI 0.70-0.96]).¹⁹ At the end of the study, weight gain was significantly lower with Gla-300 than with Gla-100, and insulin dose was 17% higher with Gla-300 than with Gla-100.¹⁹ An analysis of morning versus evening injection time in this study found no clinically meaningful differences in outcomes.¹⁹

The new Gla-300 formulation (Toujeo; Sanofi US LLC, Bridgewater, NJ) is available in a disposable pen device (SoloSTAR; Sanofi US LLC, Bridgewater, NJ) that provides insulin in single-unit increments up to a maximum dose of 80 units per injection; each pen contains 1.5 mL (equivalent to 450 units) of insulin and are supplied 3 to a box. The dose is selected on the dial and no volume calculations or conversions are needed.

The impact of flexibility in the timing of doses of Gla-300 was investigated in two 3-month extension substudies to the EDITION 1 and EDITION 2 trials.²⁰ After the initial 6-month study period in the Gla-300 arms of EDITION 1 and 2, patients were randomized to either the fixed-treatment arm (24-hour interval) or the flexible treatment arm (24 hours $\pm$ up to 3 hours interval). In the individual studies and in a pooled analysis of these data, A1C was comparable to the substudy baseline in both the fixed- and flexible-treatment arms and between arms; fasting plasma glucose (FPG) and the percentage of patients experiencing ≥ 1 nocturnal or any time of day confirmed or severe hypoglycemia event(s) were also comparable (Table 1).²⁰ These results suggest that greater variability in injection timing (24 hours $\pm$ up to 3 hours), which may be seen in usual daily life, did not compromise efficacy or safety in T2D.²⁰

Insulin Degludec

Insulin degludec (Tresiba; Novo Nordisk A/S, Bagsvaerd, Denmark) is a new long-acting basal insulin. Following subcutaneous injection it forms a soluble multi-hexameric depot from which insulin degludec monomers are slowly released, leading to a prolonged action profile; albumin binding, to a lesser extent, may also contribute to the prolonged absorption kinetics.^{12,24} Insulin degludec is available in 2 formulations delivering 100 units/mL (Deg-100) and 200 units/mL (Deg-200). The Deg-200 formulation delivers the same dose as Deg-100 in one-half of the volume.²⁵ Insulin degludec was approved for use in the United States in September 2015.

Insulin degludec, similarly to Gla-300, has a PK/PD profile that is fitting for basal insulin replacement. At steady state, Deg-100 has been shown to have a flat and stable glucose-lowering action (Figure 1) with a consistent effect that extends for more than 42 hours, allowing once-daily dosing.^{26,27} The glucose-lowering effect of Deg-100 is more predictable over 24 hours than Gla-100, with less interindividual variability in day-to-day glycemic control.¹³ The

half-life of insulin degludec at steady state has been shown to be approximately 25 hours.^{13,27} An evaluation of the steady-state PK and PD profiles of Deg-100 and Deg-200 in patients with T1D showed that the 2 formulations could be considered bioequivalent, with similar PK/PD characteristics (Figure 1).¹²

The clinical efficacy and safety of Deg-100 has been evaluated in patients with T2D and T1D in the phase 3 BEGIN clinical trial program. Throughout the BEGIN program, hypoglycemia was described as "confirmed" if blood glucose was <56 mg/dL or "severe" if the patient required assistance; the nocturnal period was 00:01 to 05:59. The primary end point in these trials was to confirm noninferiority of insulin degludec to Gla-100 in reduction in A1C from baseline, with a noninferiority margin of 0.4%.

Deg-100 was investigated in patients with T1D in the BEGIN Basal-Bolus T1 trial. In this 52-week trial, Deg-100 showed comparable A1C and fasting blood glucose (FBG) reduction to Gla-100, with a comparable rate of hypoglycemia at any time of day (Table 2).²⁸ The rate of nocturnal hypoglycemia was lower with Deg-100 over both the entire study period and during the maintenance phase (Week 16 to end of study; rate ratio 0.73 [0.56 to 0.96]).²⁸ There was comparable weight gain between the treatment groups, and basal insulin dose was significantly lower with Deg-100 (Table 2).²⁸

BEGIN Basal-Bolus Type 2 was a 52-week trial of Deg-100 versus Gla-100 with mealtime insulin in patients with T2D previously treated with basal insulin.²⁹ Deg-100 showed comparable A1C and FBG reduction to Gla-100 (Table 2).²⁹ Both hypoglycemia at any time of day and nocturnal hypoglycemia were significantly lower with Deg-100 over both the entire study period (Table 2) and during the maintenance phase (Week 16 to end of study) for nocturnal events (rate ratio 0.72 [0.51 to 0.99]).²⁹ There was comparable weight gain between the treatment groups, and a significantly greater basal insulin dose with Deg-100 (Table 2).²⁹

The 2 BEGIN Flex trials (T1 and T2) compared Deg-100 in a forced flex-dosing regimen, prespecified rotating morning and evening dosing schedule (Deg-100 Flex) with Gla-100 in 26-week trials.^{30,31} Both of these trials met the noninferiority criteria for Deg-100 Flex; however, in the BEGIN Flex T1 trial A1C reduction was significantly less with Deg-100 Flex versus Gla-100 (estimated treatment difference 0.17% [95% CI 0.04-0.30]).^{30,31} There were comparable rates of hypoglycemia at any time of day in the 2 studies, and the rate of nocturnal hypoglycemia was significantly lower with Deg-100 Flex in BEGIN Flex T1 but comparable in BEGIN Flex T2 (Table 2).^{30,31} These trials also showed that as a result of the long duration of action of insulin degludec, the time of administration of Deg-100 could be varied safely (tested with a minimum of 8 hours and a maximum of 40 hours intervals) without affecting

Table 2. Phase 3 Clinical Trial Results for Insulin Degludec.

Study	BEGIN Basal-Bolus T1 ²⁸		BEGIN Basal-Bolus T2 ²⁹		BEGIN Flex T1 ³⁰		BEGIN Flex ³¹		BEGIN Once Long ³²	
Population	T1D		T2D; basal + mealtime		T1D		T2D; insulin naive or basal insulin		T2D; insulin naive	
Duration	52 weeks		52 weeks		26 weeks		26 weeks		52 weeks	
Treatment	Deg-100	Gla-100	Deg-100	Gla-100	Deg-100 Flex ^a	Gla-100	Deg-100 Flex ^a	Gla-100	Deg-100	Gla-100
n	472	157	744	133	164	164	230	229	773	257
A1c reduction, %	-0.40	-0.39	-1.10	-1.18	-0.40	-0.58	-1.28	-1.26	-1.06	-1.19
	ETD: -0.01 (-0.14 to 0.11)		ETD: 0.08 (-0.05 to 0.21)		ETD: 0.17 (0.04 to 0.30)		ETD: 0.04 (-0.12 to 0.20)		ETD: 0.09 (-0.04 to 0.22)	
FPG reduction, mmol/L	ETD: -0.33 (-1.03 to 0.36)		ETD: -0.29 (-0.65 to 0.06)		ETD: -0.05 (-0.85 to 0.76)		ETD: -0.42 (-0.82 to -0.02)		ETD: -0.43 (-0.74 to -0.13)	
Nocturnal hypoglycemia			Confirmed (<56 mg/dL) or severe (00:01 to 05:59)							
Baseline-end of study, events/patient years	4.41	5.86	1.39	1.84	6.2	10.0	0.6	0.8	0.25	0.39
Rate ratio (95% CI)	0.75 (0.59 to 0.96)		0.75 (0.58 to 0.99)		0.60 (0.44 to 0.82)		0.77 (0.44 to 1.35)		0.64 (0.42 to 0.98)	
Hypoglycemia at any time of day			Confirmed (<56 mg/dL) or severe							
Baseline-end of study, events/patient years	42.54	40.18	11.09	13.63	82.4	79.7	3.6	3.5	1.52	1.85
Rate ratio (95% CI)	1.07 (0.89 to 1.28)		0.82 (0.69 to 0.99)		1.03 (0.85 to 1.26)		1.03 (0.75 to 1.40)		0.82 (0.64 to 1.04)	
Weight change, kg, mean	1.8	1.6	3.6	4.0	1.2	1.6	1.5	1.6	2.4	2.1
	P = .62				P = NS		P = NS		P = .28	
Basal insulin dose at end of study, mean units/kg	0.35 (SE 0.01)	0.39 (SE 0.02)	0.75 (SD 0.43)	0.69 (SD 0.40)	0.42 (SD 0.25)	0.42 (SD 0.23)			0.59	0.60
	ETR 0.86 (0.81 to 0.92)		ETR 1.08 (1.01 to 1.15)							

Abbreviations: CI, confidence interval; ETD, estimated treatment difference; ETR, estimated treatment ratio; FPG, fasting plasma glucose; n, number of patients; NS, not significant; SD, standard deviation; T1D, type 1 diabetes; T2D, type 2 diabetes.

^aFlex, prespecified rotating morning and evening dosing schedule.

either glucose control or hypoglycemia risk compared with fixed daily administration times of Deg-100 and Gla-100 in both T1D and T2D patients—these extremes of dosing, however, are not recommended in clinical practice.^{30,31}

The BEGIN Once Long trial compared Deg-100 to Gla-100 in insulin-naïve patients with T2D.³² Deg-100 showed comparable A1C reduction and greater FBG reduction compared to Gla-100.³² Hypoglycemia at any time of day was comparable between the treatment groups, while nocturnal hypoglycemia was significantly lower with Deg-100 over both the entire study period (Table 2) and during the maintenance phase (Week 16 to end of study; rate ratio 0.51 [0.32 to 0.81]).³² There was comparable weight gain between the treatment groups, and insulin dose at the end of the study did not differ (Table 2).³²

In the BEGIN series of trials comparing Deg-100 to Gla-100, Deg-100 exhibited numerically greater FPG reduction but a numerically lower A1C reduction versus Gla-100, although these differences were generally not significant.³³

The efficacy and safety of Deg-200 has also been assessed as part of the BEGIN clinical trial program. The BEGIN LOW VOLUME trial compared once-daily Deg-200 with Gla-100 in insulin-naïve patients with T2D inadequately controlled on OADs.³⁴ At the end of the study, Deg-200 and Gla-100 showed comparable A1C reduction, with a significantly greater FBG reduction with Deg-200 compared with Gla-100 (−67 vs −61 mg/dL; estimated treatment difference −7.56; $P = .02$); rates of confirmed or severe hypoglycemia, either nocturnal or at any time of day, were similar between the 2 groups.³⁴ The BEGIN: COMPARE trial compared Deg-200 with Deg-100 in patients with T2D treated with basal insulin and OADs.³⁵ At the end of the study, A1C values in each group were comparable (Deg-200, 7.3%; Deg-100, 7.5%), and the 2 groups had comparable rates of confirmed or severe hypoglycemia at any time of day or night.³⁵

An additional cardiovascular safety study of Deg-100 (DEVOTE; NCT01959529) in patients with T2D who are at high risk of CV events initiated in 2013 at the request of the Food and Drug Administration and is expected to complete in the second half of 2016.

Insulin degludec is available in a pen device (FlexTouch; Novo Nordisk A/S, Bagsvaerd, Denmark) as either Deg-100 (containing 300 units of insulin degludec in 3 mL that provides 1-unit increments from 1 to 80 units) or Deg-200 (the same device but containing 600 units of insulin degludec in 3 mL that provides 2-unit increments from 2 to 160 units). Deg-100 is supplied in packs of 5 pens, and Deg-200 is supplied in packs of 3. For both, the dose can be selected on the dial so no volume calculations or conversions are required (as with the SoloSTAR device).³⁶

It is important to note that Gla-300, Deg-100, and Deg-200 are all basal insulin formulations that provide basal coverage with once-daily injection. Prandial excursions in

blood glucose should be covered with alternative therapy options, if needed. These insulins should not be confused with regular human insulin 500 units/mL (U-500), which has clinical use as an insulin to cover both basal and prandial components in patients who require high insulin doses, but is not a basal insulin. Regular human insulin U-500 is more concentrated than conventional regular human insulin 100 units/mL (U-100) by a factor of 5. This difference allows for subcutaneous delivery of the same dose of insulin in 20% of the volume.³⁷ Compared with the regular human insulin U-100 formulation, regular human insulin U-500 has a different PK/PD profile. In obese but otherwise healthy subjects, the maximal glucose-lowering response is lower with regular human insulin U-500 than with regular human insulin U-100, and regular human insulin U-500 has a longer duration of action.³⁸ Regular human insulin U-500 has a peak glucose-lowering effect similar to that of regular human U-100, but the duration of its effect is more like that of NPH insulin: around 12 hours.³⁸ However, it is important to note that despite its longer duration of action, regular human insulin U-500 is a prandial insulin, and should be taken 30 minutes before a meal.^{38,39} The modified PK profile of regular human insulin U-500 allows patients who require high doses of prandial insulin to administer this higher dose in a smaller volume of insulin, which has practical advantages for patients and may reduce the discomfort associated with large injection volumes.

Conclusions

The goal of basal insulin treatment is to provide replacement insulin coverage that closely mimics normal basal insulin secretory patterns and provides stable glycemic control throughout a 24-hour period without a significant risk of hypoglycemia. The newest basal insulin analogs, Gla-300 and insulin degludec, offer improved PK and PD characteristics compared with Gla-100. Gla-300 has altered absorption kinetics compared to Gla-100, with a slower release from the subcutaneous injection depot. With a longer half-life and less within-patient variability in response than Gla-100, Gla-300 has a consistent and prolonged duration of action of more than 24 hours.^{9,11} Insulin degludec (an insulin that forms a soluble depot of multi-hexamers on injection which are then slowly released) also has a favorable PK/PD profile with less within-patient variability compared to Gla-100, as well as a prolonged duration of action (more than 24 hours) and a flat and stable action profile.^{26,27} As a consequence of these changes in PK/PD parameters, and with the slower onset and longer half-life compared with Gla-100, it is recommended to titrate the doses of Gla-300 or insulin degludec no more frequently than every 3 to 4 days.^{40,41} These improved PK/PD properties have led to once-daily basal insulins with comparable A1C reductions and comparable, or improved, levels of hypoglycemia

compared to Gla-100. With these clinical advantages, these novel basal insulins may provide useful therapeutic options for a range of patients with T1D or T2D.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Goldman: Speakers' bureau for Novo Nordisk and Sanofi; Consultant for Becton Dickinson. White: Advisory board for Sanofi; Consultant for Becton-Dickenson.

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