Long-acting insulin side-by-side comparison

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Evidence summary

Introduction

Currently there are 6 long-acting (LA) insulin analog products approved by the U.S. Food and Drug Administration (FDA): insulin detemir (Levemir), insulin glargine (Lantus, Semglee, Basaglar, Toujeo), and insulin degludec (Tresiba). All products are indicated to improve glycemic control in type 1 diabetes mellitus (T1DM) in adults and pediatric patients and type 2 diabetes mellitus (T2DM) in adults. All LA insulin analogs have a protracted duration of action, which is achieved through structural modifications of the primary amino acid sequence of human insulin. The prolonged action of insulin glargine is due to formation of slow dissolving microprecipitates after subcutaneous injection while insulins detemir and degludec achieve a protracted duration through self-association and albumin binding after subcutaneous injection. In general, LA insulin analogs are associated with flatter, more consistent insulin plasma concentrations than NPH insulin.

Historically, insulin products have been approved by the FDA as drugs via new drug applications (NDAs) submitted through section 505 of the Food Drug and Cosmetic Act. The Biologics Price Competition and Innovation Act, the legislation that established the biosimilar approval pathway, included a provision that transitioned biological products previously approved as NDAs to biological license applications (BLAs) on March 23, 2020. As a result of the transition, originator insulins, like other biologics, are now subject to biosimilar development.

Prior to the transition, 2 follow-on insulin glargine products (Basaglar and Semglee) were submitted or approved as NDAs pursuant to section 505(b)(2) – an abbreviated new drug approval pathway. Because both were originally submitted as NDAs, they are now considered insulin glargine biologics licensed under separate BLAs. On July 28, 2021, the FDA approved insulin glargine-yfgn (Semglee) as the first interchangeable biologic and the first biosimilar to an insulin product. While non-biosimilar Semglee is currently marketed, it is expected that interchangeable, biosimilar Semglee will replace the non-biosimilar Semglee as the marketed product in late 2021.

Guidelines

The American Diabetes Association (ADA) guidelines recommend the utilization of a basal insulin to regulate overnight, fasting glucose in T1DM. For T2DM patients, use of a basal insulin is recommended once the progression of the disease overcomes the effect of other anti-diabetic agents. The principal effect of adding basal insulin to other anti-diabetic agents is to limit hyperglycemia overnight and between meals. The American Association of Clinical Endocrinologists and American College of Endocrinology provide similar recommendations to that of the ADA. The available guidelines do not recommend a specific LA insulin analog, stating the choice should be individualized focusing on patient-specific considerations, including cost.

Clinical Efficacy

Detemir vs. glargine

There are multiple published comparisons of insulins glargine and detemir. While results of most controlled comparisons suggest both insulins produce similar reductions in HbA1c in T1DM and T2DM, the optimal dose and frequency of insulin detemir to achieve similar glycemic control is controversial. In most controlled studies, patients treated with insulin detemir required higher doses and twice-daily administration. Many attribute the differences in doses and frequency between the insulins to flawed study designs; however, a growing body of evidence in the heterogeneous T2DM population supports the contention that the 2 insulins are not reliably interchangeable on a unit to unit basis or at the same dosing frequency. Considered together, results of controlled and observational data indicate someT2DM patients may require higher doses and/or more frequent administration with insulin detemir than with insulin glargine to achieve comparable glycemic control. Whether or not the same is true in the more homogenous T1DM population is unknown as there is a paucity of observational data comparing the insulins in this population.

Degludec vs. glargine or detemir

Insulin degludec effectively lowers glucose levels among T1DM and T2DM patients to a similar extent as insulin glargine or insulin detemir. Pivotal comparative trials were treat-to-target and not unexpectedly, once daily insulin degludec was noninferior to once-daily insulin glargine and once- or twice-daily insulin detemir. Other key glycemic outcomes, including percent of patients achieving the HbA1c goal of < 7% did not differ significantly between insulin degludec and insulin glargine. Fasting plasma glucose (FPG) was significantly

reduced with insulin degludec in basal only trials, but not in basal bolus trials. In basal only trials, the mean FPG difference between insulin degludec and insulin glargine was 7.6 to 7.7 mg/dL. Of note, differences in administration time between insulins degludec and glargine may have contributed to differences in FPG.

Follow-on glargine or glargine-yfgn vs. reference glargine

Results of comparative clinical research suggest that follow-on insulin glargine and insulin glargine-yfgn are pharmacokinetically and pharmacodynamically equivalent to reference insulin glargine in healthy subjects and are noninferior to insulin glargine for reduction in HbA1c in adult patients with T1DM and T2DM on a unit-to-unit basis. Evidence suggests that there are no safety or efficacy concerns for a single transition from reference insulin glargine to follow-on insulin glargine or for switching between reference insulin glargine and insulin glargine-yfgn.

Convenience factors

Dose and duration

Insulin degludec has the shortest duration of action of the LA insulin analogs with a dose-dependent duration of action that ranges from 17 to 24 hours. Insulin glargine 100 units/mL has a concentration/time profile that is relatively constant over 18 hours and demonstrates a slow decrement over 20 to 24 hours, making it an almost 24-hour basal insulin in most patients. Concentrated insulin glargine 300 units/mL and insulin degludec have the longest duration of action at 30 hours and 42 hours, respectively. Except for insulin detemir that may require twice daily dosing in some patients, LA insulin analogs are dosed once daily. Due to its ultra-long half-life, insulin degludec is the first basal insulin that can be given at varying dosing intervals without reducing glycemic efficacy. This may be an advantage among patients who need greater flexibility in administration time. The other LA insulin analogs can be given at any time of the day but should be given at the same time each day.

Most of the LA insulin analogs can be converted on a unit-to-unit basis. Concentrated insulin glargine 300 units/mL has lower bioavailability than insulin glargine 100 units/mL; therefore, it is likely a higher dose of insulin glargine 300 units/mL vs. insulin glargine 100 units/mL will be needed to achieve the same glycemic control. In trials, patients treated with twice-daily insulin detemir require higher doses than those treated with once-daily insulin glargine.

Dosage forms

All LA insulin analogs are supplied as single-patient, prefilled pens. In addition, insulin detemir, insulin glargine 100 units/mL (Lantus), insulin glargine-yfgn (Semglee), and insulin degludec (Tresiba) are supplied as multi-dose vials. In an inpatient setting, insulin pens or vials may present safety and operational challenges that are unique to each. Insulin degludec and insulin glargine are supplied as concentrated 200 unit/mL and 300 unit/mL formulations, respectively. The more concentrated formulations allow higher doses of basal insulin to be administered per volume used, which may be more convenient and comfortable for patients who require larger basal insulin doses. These more concentrated formulations are supplied only as prefilled pens to prevent medication errors.

Safety

Nocturnal hypoglycemia

Insulin glargine 300 units/mL and insulin degludec are associated with less intra-patient variability in plasma insulin concentrations compared with insulin glargine 100 units/mL and as a result, both are associated with modest decreases in the incidence of nocturnal hypoglycemia. The incidence of nocturnal hypoglycemia was significantly lower with the more concentrated formulation of insulin glargine in 2 of 3 head-to-head comparisons; however, in these trials the upper bound of the 95% confidence interval for the difference between formulations was 0.93 and 0.99.

Across the BEGIN trials, the definitions for confirmed, severe, and nocturnal hypoglycemia were standardized and a meta-analysis of 7 BEGIN trials was preplanned to assess the superiority of insulin degludec for frequency and rates of hypoglycemic episodes. During the entire trial treatment period (titration and maintenance period), there were no significant differences between insulin degludec and glargine in the T1DM population for overall confirmed, nocturnal confirmed, and severe hypoglycemic episodes. Among the T2DM population, including both insulin-naïve and experienced patients, insulin degludec was associated with a significant decrease in the rate of overall confirmed and nocturnal confirmed hypoglycemic episodes, but not severe episodes. In the subgroup of insulin-naïve T2DM patients, results were similar to the overall T2DM population, but in this subgroup, insulin degludec was also associated with a decreased incidence of nocturnal confirmed hypoglycemic episodes. During its initial review, the FDA questioned the claim that insulin degludec is associated with a lower incidence of

hypoglycemia, suggesting that a difference between basal insulins was observed only among the population at lowest risk of hypoglycemia, namely T2DM patients on basal insulin only.

Other adverse events

In general, other potential adverse events – weight gain, fluid retention, injection site reactions, allergic reactions, and immunogenicity – do not appear to be different to a clinically relevant extent among the different LA insulin analogs. Insulin detemir may be associated with less weight gain than insulin glargine, but it may lose some of its benefit if dosed twice daily.

Conclusions

While there may be subtle differences in duration, hypoglycemia occurrence, insulin dose, and weight gain among the LA insulin analogs, in outpatient practice, the choice among insulin analogs is likely to be more heavily influenced by cost and insurance coverage than differences among insulins. For inpatient practice, dosage form in addition to cost may influence formulary decisions.

Long-acting insulin side-by-side comparison

	Brand name (generic name)					
	Levemir (insulin detemir)	**Lantus (insulin glargine)**	**Semglee (insulin glargine-yfgn)**	**Basaglar (insulin glargine)**	**Toujeo (insulin glargine)**	**Tresiba (insulin degludec)**
Manufacturer	Novo Nordisk	Sanofi Aventis	Mylan/Biocon	Eli Lily and Company	Sanofi Aventis	Novo Nordisk
Approval date	October 2005	April 2000	June 2020, July 2021	December 2015	February 2015	September 2015
Initial approval pathway	NDA, 505(b)(1)	NDA, 505(b)(1)	• June 2020 – BLA, 351a • July 2021 – BLA, 351K	NDA, 505(b)(2)	NDA, 505(b)(2)	NDA, 505(b)(1)
License type	351(a)	351(a)		351(a)	351(a)	351(a)
Biosimilar	No	No	Yes (interchangeable)	No	No	No
FDA-approved indication	To improve glycemic control in DM					
Adults	T1DM, T2DM	T1DM, T2DM	T1DM, T2DM	T1DM, T2DM	T1DM, T2DM	T1DM, T2DM
Pediatrics	T1DM, T2DM (≥2 y)	T1DM	T1DM	T1DM (≥ 6 y)	T1DM, T2DM (≥ 6 y)	T1DM, T2DM (≥ 1 y)
Pharmacology	The primary activity of insulin is the regulation of glucose metabolism. Insulins exert their specific action through binding to insulin receptors. Receptor-bound insulin lowers blood glucose by facilitating cellular uptake of glucose into skeletal muscle and fat and by inhibiting the output of glucose from the liver. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis, and enhances protein synthesis.					
Mechanism of extended action	Dihexamerization and albumin binding.	Decreased solubility at neutral subcutaneous tissue pH, resulting in microprecipitation with subsequent slow release of insulin monomers.				Dihexamerization and albumin binding.
Pharmacokinetics						
Onset	0.8 to 2 h	1.1 h			6 h	1 h
Duration	6 to 24 h (dose dependent)	24 h			> 24 h (30 h)	> 24 h (42 h)
Contraindications	Hypersensitivity; use during episodes of hypoglycemic.					
Warnings/precautions	• Never share pens between patients, even if the needle is changed. • Changes in insulin regimen should be made under medical supervision. The frequency of blood glucose monitoring should be increased after changes. • Hypoglycemia may be life-threatening. Increase glucose monitoring with changes to co-administered medications, meals, or lifestyle. • Accidental mix-ups between insulins may occur and lead to hypoglycemia. Always check label of insulin prior to injection. • Monitor potassium levels in patients at risk for hypokalemia and treat if indicated. • Severe, life-threatening hypersensitivity, including anaphylaxis, may occur. Renal or hepatic impairment may require dose adjustment. • Fluid retention and heart failure can occur with concomitant thiazolidinedione.					

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Adverse events	**Most common**: Hypoglycemia, allergic reactions, injection site-reactions, lipodystrophy, rash, pruritus, edema, and weight gain.					
Drug interactions	• Following may **reduce** blood-glucose-lowering effect: corticosteroids, danazol, diuretics, sympathomimetic agents (eg, epinephrine, albuterol, terbutaline), isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (eg, in oral contraceptives). • Following may **increase** blood-glucose-lowering effect: oral antidiabetic drugs, angiotensin-converting enzyme inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, propoxyphene, salicylates, somatostatin analog (eg, octreotide), and sulfonamide antibiotics. Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia. In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine, and reserpine, the signs of hypoglycemia may be reduced or absent. Alcohol may increase hypoglycemia.					
Storage/stability considerations						
Unopened vial or pen	• Refrigerated (2°-8°C) until expiration date. • Room temperature (below 30°C) for 42 d. • Do not freeze or use if product has been frozen.	• Refrigerated (2°-8°C) until expiration date. • Room temperature (below 30°C) for 28 d. • Do not freeze or use if product has been frozen.			Refrigerated (2°-8°C) until expiration date.	• Refrigerated (2°-8°C) until after expiration date. • Room temperature (below 30°C) for 56 d. • Do not freeze or use if product has been frozen.
Opened (in-use) vial	Refrigerated or at room temperature for 42 d.	Refrigerated or at room temperature for 28 d.		N/A	N/A	Refrigerated or at room temperature for 56 d.
Opened (in-use) pen	• Room temperature for up to 42 d. • Do not refrigerate.	• Room temperature for 28 d. • Do not refrigerate.			• Room temperature for 56 d. • Do not refrigerate.	Refrigerated or at room temperature for 56 d.

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Dosage forms							
100 units/mL (U-100)	Vials (multi-dose)	10 mL	10 mL	10 mL	N/A	NA	10 mL
	Prefilled pen (single patient use)	3 mL FlexTouch pen (1-unit increment)	3 mL SoloStar pen (1-unit increment)	3 mL prefilled pen (1-unit increment)	3 mL KwikPen (1-unit increment)	N/A	3 mL FlexTouch pen (1-unit increment)
200 units/mL (U-200)		N/A	N/A	N/A	N/A	N/A	Prefilled pen, single patient use: 3 mL FlexTouch pen (2-unit increment)
300 units/mL (U-300)		N/A	N/A	N/A	N/A	Prefilled pen, single patient use • 1.5 mL SoloStar pen (1-unit increment) • 3 mL SoloStar pen (2-unit increment)	N/A
Combination products		N/A	Insulin glargine and lixisenatide (Soliqua) 100 units/3.3 mg per mL, supplied as a 3 mL single patient pen	N/A	N/A	N/A	Insulin degludec and liraglutide (Xultophy) 100 units/3.6 mg per mL, supplied as a 3 mL single patient pen (1-unit increment)
Dosage							
T1DM insulin-naive		• Approximately 1/3 to 1/2 of the insulin total daily dose. • As a rule, 0.2 to 0.4 units/kg can be used to calculate the initial insulin total daily dose.					
T2DM insulin-naive		0.2 units/kg or up to 10 units daily					
Patients already on insulin therapy		Transitioning from: • Insulin glargine 100 units/mL: 1:1	Transitioning from: • Insulin glargine 100 units/mL: 1:1 unit to unit conversion • Insulin glargine 300 units/mL: Initial dose is 80% of insulin glargine 300 units/mL dose.			Transitioning from: • Once-daily LA insulin: Initiate at the same unit	• Adults with T1DM or T2DM transitioning from LA or intermediate-

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	unit to unit conversion. • NPH insulin: 1:1 unit to unit conversion. However, some patients may require more detemir than NPH.	• Once-daily NPH insulin: Initial dose of insulin glargine is the same as the dose of NPH that is being discontinued. • Twice-daily NPH insulin: Initial dose of insulin glargine is 80% of the total NPH dose that is being discontinued.			dose as the once-daily LA insulin dose. If converting from insulin glargine 100 units/mL, expect a higher daily dose of insulin glargine 300 units/mL. • Twice-daily LA or intermediate-acting insulin: Initial dose of insulin glargine is 80% of total daily NPH or insulin detemir twice daily.	acting insulin: 1:1 unit to unit conversion. • Pediatrics with T1DM or T2DM transitioning from LA or intermediate-acting insulin: Initiate at 80% of the total daily LA or intermediate-acting insulin unit dose.
Administration						
Co-administration	• Do not dilute or mix with other insulin preparations. • Do not administer subcutaneous via an insulin pump, intramuscularly, or intravenously because of the risk of severe hypoglycemia.					
Frequency per day	Once or twice	Once	Once	Once	Once	Once
Time of day	• Once daily: Administer dose with the evening meal or at bedtime. • Twice daily: Administer second dose with evening meal, at bedtime, or 12 h after the morning dose.	Any time of the day, but at the same time each day.				• Adults: At any time of day. • Pediatrics: At same time each day.

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Cost (WAC)							
100 units/mL (U-100)	Vials (multi-dose)	$308.14	$283.56	$98.65	N/A	N/A	$338.95
	Prefilled pen (single patient use)	$462.21 (5 pens)	$85.06 (1 pen)	$29.60 (1 pen)	$65.27 (1 pen)	N/A	$508.43 (5 pens)
200 units/mL (U-200)		N/A	N/A	N/A	N/A	N/A	$610.11 (3 pens)
300 units/mL (U-300)		N/A	N/A	N/A	N/A	$129.57 (1 pen, 1.5 mL) $259.12 (1 pen, 3 mL)	N/A

Insulin detemir (Levemir) vs. insulin glargine (Lantus) clinical trials

- **Zhang T, Lin M, Li W, et al. *Adv Ther.* 2016;33(2):178-185.** In a randomized, crossover study of 55 hospitalized patients with T2DM, insulin detemir was compared with insulin glargine. Patients were randomized to once-daily detemir or glargine 0.2 units/kg titrated daily by 0.1 unit/kg to achieve FPG < 140 mg/dL before crossing over to the other agent. There was no difference in the 6-point PG profile for the final 24 h of receiving each agent (*P* = .308-.927). Time to achieve FPG target (4.0 ± 0.5 d vs 3.3 ± 0.4 d for detemir vs glargine; *P* = .286) and total daily dose (30.1 ± 2.4 units vs 30.1 ± 2.9 units for detemir vs glargine; *P* = .999) were similar. Following the crossover, there were 6 hypoglycemic events (< 70 mg/dL) among the patients switched to detemir.
- **Meneghini L, Kesavadev J, Demissie M, Nazeri A, Hollander P. *Diabetes Obes Metab.* 2013;15(8):729-736**. In a 26-wk, multinational, randomized, open-label, treat-to-target trial 457 insulin-naïve T2DM patients were randomized to once-daily insulin detemir or insulin glargine. Change in HbA1c from baseline was 0.48% with detemir and 0.74% with glargine (estimated difference: 0.30; 95% CI, 0.14 to 0.46). Noninferiority was not confirmed. Proportion reaching HbA1c ≤ 7% was 38% and 53% for detemir and glargine, respectively (*P* = .026). Hypoglycemic events were lower with detemir (3.19 episodes/y) than glargine (4.41 episodes/y; *P* = .034). Mean insulin doses at study end were 57 units with detemir and 51 units with glargine (*P* = .0208).
- **Swinnen SG, Dain MP, Aronson R, et al. *Diabetes Care.* 2010;33(6):1176-1178**. In a 24-wk, multicenter, randomized, open-label, noninferiority trial, 973 insulin-naïve T2DM patients were randomized to twice-daily insulin detemir or once-daily insulin glargine. Insulin detemir was deemed noninferior to insulin glargine based on the proportion of patients achieving hemoglobin HbA1c of < 7% without symptomatic hypoglycemia—25.6% and 27.5%, respectively (difference: 1.85%; 95% CI, -3.78% to 7.48%). Insulin doses were significantly higher with detemir (76.5 ± 50.5 units/d) than with glargine (43.5 ± 29.0 units/d; *P* < .001). Study discontinuation due to adverse events was higher among patients taking detemir (22 patients) than those taking glargine (7 patients; *P* = .005).
- **Heller S, Koenen C, Bode B. *Clin Ther*. 2009;31(10):2086-2097**. In an open-label, randomized, treat-to-target, noninferiority trial, 443 patients with T1DM were treated with once- or twice-daily insulin detemir or once-daily insulin glargine. At the end of 52 wk, detemir was noninferior to glargine based on the change in HbA_{1c} from baseline (mean difference: 0.01%; 95% CI, -0.13 to 0.16). There were no significant differences between detemir and glargine in the proportion of patients achieving a HbA1c ≤ 7% (33% vs. 30.4%), mean FPG (8.58 vs. 8.81 mmol/L), weight gain (0.36 kg vs. 0.42 kg), or the number of hypoglycemia episodes per patient per year (53.6 vs. 57.3). The majority of patients received twice-daily detemir (65.8%).
- **Raskin P, Gylvin T, Weng W, Chaykin L. *Diabetes Metab Res Rev*. 2009;25(6):542-548**. In an open-label, randomized, noninferiority trial, 385 patients with T2DM were treated with once- or twice-daily insulin detemir or once-daily glargine. At 26 wk, the change in HbA1c from baseline was 1.1% and 1.3% in the detemir and

glargine groups, respectively, meeting noninferiority criteria. Change in FPG did not differ between treatment groups (detemir -43.2 mg/dL, glargine -38.7 mg/dL) nor did incidence of all hypoglycemic events (detemir 76.2%, glargine 74.8%). The difference in weight gain was 1.37 kg in favor of insulin detemir.

- **Hollander P, Cooper J, Brenghoj J, Pederson CB. *Clin Ther*. 2008;30(11):1976-1987**. In a 52-wk, multicenter, randomized, open-label, noninferiority trial, the efficacy and safety profiles of once-or twice-daily insulin detemir and once-daily glargine were compared in patients with T2DM treated with or without OADs. After 52 wk, the mean HbA1c values were 7.19% with detemir (n = 214) and 7.03% with glargine (n = 105) (mean difference, 0.17%; 95% CI, -0.07 to 0.40). There were no significant differences between detemir and glargine for the following endpoints: mean FPG, proportion of patients achieving HbA1c ≤ 7%, and major hypoglycemic events. Mean weight gain was significantly less with detemir (2.8 kg) compared with glargine (3.8 kg; mean difference, -1.04; 95% CI, -2.08 to -0.01).
- **Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Schernthaner G. *Diabetologia*. 2008;51(3):408-416**. In a 52-wk, multicenter, randomized, open-label, noninferiority trial in 582 insulin-naïve patients with T2DM, treatment with once-or twice-daily insulin detemir or once-daily insulin glargine decreased baseline HbA1c by 1.5% to 7.2% in the insulin detemir group and to 7.1% in the insulin glargine group *(P* > .05). There were no significant differences between treatment groups in clinic FPG (detemir -127.8 mg/dL; glargine -126 mg/dL), proportion of patients achieving HbA1c ≤ 7% (detemir -33%; glargine -35%), or relative risk of overall or nocturnal hypoglycemia. The mean daily dose of insulin detemir was higher than insulin glargine (0.78 units/kg vs.0.44 units/kg) and injection-site reactions were more common with insulin detemir (4.5% vs. 1.4%).
- **Pieber TR, Treichel HC, Hompesch B, et al. *Diabet Med*. 2007;24(6):635-642**. In a 26-wk, multicenter, randomized, open-label trial, 320 patients with T1DM treated with either twice-daily insulin detemir or once-daily insulin glargine experienced HbA1c reductions of 0.7% and 0.6%, respectively. FPG, measured at home, was significantly lower in the insulin glargine group compared with the insulin detemir group (126 mg/dL vs.138.6 mg/dL, respectively; *P* < .001). Severe hypoglycemic events requiring assistance were significantly less frequent in the insulin detemir group (1.9%) than the insulin glargine group (7.8%) during wk 7 through wk 26 *(P* = .047 for intergroup comparison). Similarly, symptomatic nocturnal events not requiring assistance were significantly less frequent in the insulin detemir group (19%) than the insulin glargine group (24%) during the same time period *(P* = .043 for intergroup comparison).

Insulin glargine-yfgn or MYL-1501D (Semglee) vs. reference insulin glargine (Lantus) clinical trials

- **INSTRIDE 1 trial. Blevins TC, Sun B, Ankersen M. *Diabetes Obes Metab*. 2018;20(8):1944-1950**. INSTRIDE 1 trial was a multicenter, randomized, open-label, parallel-group, phase 3 trial, in which adult patients with T1DM, after a 4-wk screening and 6-wk run-in period, were randomized (1:1) to once-daily injections of MYL-1501D (n = 280) or reference insulin glargine (n = 278) in the morning or evening in combination with mealtime insulin lispro 3 times a day. Dose adjustments were done weekly during the first 4 wks after randomization and then only if required for patient safety. Basal insulin was adjusted to a 71 to 130 mg/dL fasting SMPG goal and insulin lispro was adjusted to a postprandial glucose <180 mg/dL. The primary outcome was change in HbA1c at wk 24. Noninferiority was confirmed if the upper boundary of the two-sided 95% CI was ≤0.4%. At 24 wks, noninferiority was demonstrated by the mean change in HbA1c of 0.14% in the MYL-1501D group vs. 0.11% in the reference insulin glargine group (treatment difference: 0.03%; 95% CI, -0.066 to 0.117). The mean change in basal insulin dose at 52 wks was 0.0128 units/kg in the MYL-1501D group and 0.0043 units/kg in the reference insulin glargine group. Fasting plasma glucose levels were similar in both groups. Self-monitored plasma glucose levels declined, and a similar body weight increase was observed in both treatment groups. Hypoglycemia (≤70 mg/dL) was observed in 55% of patients in the MYL-1501D group and 61.2% in the reference insulin glargine group. The incidence of nocturnal hypoglycemic events was 2.9% in the MYL-1501D group (vs. 2.5% for the reference insulin glargine group).
- **INSTRIDE 2 trial. Blevins TC, Barve A, Sun B, et al. *Diabetes Obes Metab*. 2019;21(1):129-135**. In a multicenter, open-label phase 3 trial, 560 insulin-naïve and non-insulin naïve patients with T2DM who were taking OADs at baseline were randomized 1:1 to receive MYL-1501D or reference insulin glargine. For insulin-naïve patients (41% of patients at baseline), the recommended starting dose was 10 units once daily and was adjusted weekly to attain a fasting preprandial SMPG of 70 mg/dL to 130 mg/dL during the first 12 wks of the trial. From wk 12 to trial end, minimal titration of basal insulin occurred. For the primary endpoint, MYL-1501D was noninferior to reference insulin glargine for the change in HbA1c from baseline to wk 24 because the upper boundary of the two-sided 95% CI for the treatment difference was ≤ 0.4% (treatment difference: 0.06%; 95% CI, -0.10 to 0.22%). Secondary efficacy endpoints that included mean (SD) change from baseline in FPG at week 24 (MYL-1501D: -0.74 (3.11) mmol/L vs. reference: -1.05 (3.04) mmol/L; *P* = .071), mean weight gain at wks 12 and 24, and mean (SD) dose of daily basal

insulin at wk 24 (MYL-1501D: 0.37 (0.21) units/kg vs. reference: 0.38 (0.23) units/kg) were not significantly different between treatment groups. Treatment-related hypoglycemia (SMPG ≤70 mg/dL) was the most common adverse event in both groups and occurred in 62 (22.5%) and 56 (19.9%) patients in the MYL-1501D and reference glargine groups, respectively. The rate of overall, anytime, and nocturnal hypoglycemia did not differ between groups. A similar percentage of patients in the MYL-1501D and reference glargine groups had a negative response for total ADAs (63.4% vs. 61.3%, respectively) and insulin cross-reactive antibodies (62.7% vs. 62.8%, respectively).

- **INSTRIDE 3 trial. Blevins TC, Barve A, Raiter Y, et al. *Diabetes Obes Metab*. 2020;22(3):365-372**. In a multicenter, open-label phase 3 trial, 127 participants who completed 52 wks of therapy with reference glargine in the INSTRIDE 1 trial were randomized 1:1 to remain on reference glargine (n = 63) for 36 wks or to switch between MYL-1501D (wks 0-12, wks 24-36) and reference glargine (wks 12-24) every 12 wks (n = 64). All participants received premeal insulin lispro. Initial doses of basal insulin were individualized to patient's PG. At 36 wks, the primary endpoint, least square means change in HbA1c from baseline to wk 36 was -0.05 for the switching group and -0.06 for the reference insulin glargine group. The boundaries of the 95% CI for the treatment difference were ±0.4%, establishing equivalence between the switching and non-switching groups. Throughout treatment, HbA1c remained relatively consistent and there were no statistically significant changes from baseline or between treatment groups at any point. In the switching group, there was a statistically significant increase of 0.01 units/kg in the basal insulin dose from baseline to week 4 that did not occur in the reference insulin glargine group, but the baseline daily insulin dose was higher in the reference glargine group at baseline (0.36 units/kg vs. 0.32 units/kg for switching group). There was a single statistically significant difference between treatment groups during wks 24-36, but the difference - 0.019 units/kg (95% CI, 0.007 to 0.031 units/kg) – was deemed to be clinically nonsignificant. Rates of treatment-emergent adverse events and anytime or nocturnal hypoglycemic events did not differ between treatment groups. Although nocturnal hypoglycemic events were numerically greater in the switching treatment group, the numeric imbalance occurred during all treatment periods, including the treatment period with reference insulin glargine. The incidence of treatment-emergent ADA response was similar between groups; 14.1% for the treatment switching group and 14.3% for the reference glargine group.

Follow-on insulin glargine (Basaglar) vs. insulin glargine (Lantus) clinical trials

- **Blevins TC, Dahl D, Rosenstock J, et al. *Diabetes Obes Metab.* 2015;17(8):726-733**. In a 52-wk, multicenter, randomized, open-label trial conducted in 535 patients with T1DM, follow-on insulin glargine was noninferior to insulin glargine, as assessed by the mean difference in change in HbA1c from baseline to wk 24 (difference: 0.108%; 95% CI, -0.002 to 0.219; *P* > .05). SMPG values were significantly lower with follow-on insulin glargine at bedtime (24 wk, 52 wk) and at 0:300 h (24 wk), but differences were not clinically meaningful. At wk 24, overall rates (events/patient/y) of total (86.5 ± 77.3 vs. 89.2 ± 80.1), nocturnal (18.3 ± 23.6 vs. 18.4 ± 21.5), and severe hypoglycemia (0.06 ± 0.52 vs. 0.09 ± 0.50) did not differ significantly between follow-on insulin glargine and insulin glargine, respectively. Insulin doses, weight change, and incidence of detectable antibodies were similar between groups at wks 24 and 52.
- **Rosenstock J, Hollander P, Bhargava A, et al. *Diabetes Obes Metab*. 2015;17(8):734-741**. In a 24-wk, multicenter, randomized, double-blind trial conducted in 756 insulin-naïve and insulin-experienced T2DM patients, follow-on insulin glargine demonstrated noninferiority to insulin glargine based on the change from HbA1c from baseline to wk 24 at both the 0.4% and 0.3% noninferiority margin (wk 24 difference: 0.052%; 95% CI, -0.070 to 0.175). SMPG profile was significantly lower with follow-on insulin glargine at the midday premeal assessment at wk 24 *(P* = .040). At wk 24, overall rates (events/patient/y) of total (21.3 ± 24.4 vs. 22.3 ± 28.2), nocturnal (7.6 ± 11.8 vs. 8.1 ± 14.6), and severe hypoglycemia (0.04 ± 0.66 vs. 0.01 ± 0.16) did not differ significantly between follow-on insulin glargine and insulin glargine, respectively. Insulin doses, weight change, and incidence of detectable antibodies were similar between groups at wk 24.

	Brand name (generic name)					
	Levemir (insulin detemir)	Lantus (insulin glargine)	Semglee (insulin glargine-yfgn)	Basaglar (insulin glargine)	Toujeo (insulin glargine)	Tresiba (insulin degludec)
Insulin glargine 300 units/mL (Toujeo) vs. insulin glargine 100 units/mL (Lantus) clinical trials						

- **Riddle MC, Bolli GB, Zieman M, et al. *Diabetes Care*. 2014;37(10):2755-2762**. EDITION 1 trial was a multicenter, randomized, open-label, parallel-group, phase 3 trial, in which adult patients with T2DM were randomized (1:1) to once-daily injections of insulin glargine 300 units/mL (n = 404) or 100 units/mL (n = 400) before dinner to bedtime. Randomization was stratified by HbA1c (<8.0% and ≥8.0%) at screening. Dose adjustments were done no more often than every 3 d, with a 100 to 120 mg/dL fasting SMPG goal and were restricted by protocol. Inclusion criteria consisted of adult patients (≥18 years of age) with T2DM; treated with basal and mealtime insulin, including basal therapy ≥42 units/d of insulin glargine (100 units/mL) or NPH and mealtime therapy with insulin lispro, aspart, or glulisine with or without metformin for ≥12 mos; and a HbA1c 7.0% to 10.0%. The primary outcome was change in HbA1c after 6 mos or the last visit on treatment. Noninferiority was confirmed if the upper boundary of the two-sided 95% CI was ≤0.4%. At trial completion, the mean HbA1c was 7.25% in the 300 units/mL group vs. 7.28% in the 100 units/mL group. Noninferiority was demonstrated by the mean change in HbA1c of - 0.83% in both groups (treatment difference: - 0.00%; 95% CI, - 0.11 to 0.11%). Reductions in FPG from baseline were similar in both groups. At trial completion, 39.6% of patients in the 300 units/mL group and 40.9% of patients in the 100 units/mL group achieved HbA1c <7.0%. The final total daily dosage was 1.53 units/kg/d in the 300 units/mL group and 1.43 units/kg/d in the 100 units/mL group. SMPG profiles declined, and a body weight increase of 0.9 kg was observed in both treatment groups. Patients with ≥ 1 confirmed (≤70 mg/dL) or severe nocturnal hypoglycemic events from wk 9 to 6 mos was 36% in the 300 units/mL group vs. 46% in the 100 units/mL group (RR: 0.79; 95% CI, 0.67-0.93; *P* <.005).
- **Yki-Jarvinen H, Bergenstal R, Ziemen M, et al. *Diabetes Care.* 2014;37(12):3235-3243**. EDITION 2 trial was a multicenter, randomized, open-label, parallel-group, phase 3 trial, in which adult patients with T2DM were randomized (1:1) to once-daily injections of insulin glargine 300 units/mL (n = 403) or 100 units/mL (n = 405) administered in the evening after a 2-wk screening phase. Randomization was stratified by HbA1c (<8.0% and ≥8.0%) at screening. Inclusion criteria consisted of adult patients (≥18 years of age) with T2DM diagnosis ≥1 y before screening and ≥6 mos of basal insulin therapy, with ≥42 units/d of insulin glargine (100 units/mL) or NPH combined with OADs, and HbA1c 7.0% to 10.0%. Dose adjustments were done weekly, with a 100 to 120 mg/dL fasting SMPG goal and were restricted by protocol. The primary outcome was change in HbA1c after 6 mos or the last visit on treatment without rescue therapy. Noninferiority was confirmed if the upper boundary of the two-sided 95% CI was ≤0.4%. At trial completion, HbA1c was 7.57% in the 300 units/mL group vs. 7.56% in the 100 units/mL group. Noninferiority was demonstrated by the mean change in HbA1c of - 0.57% in the 300 units/mL group vs. - 0.56% in the 100 units/mL group (treatment difference: - 0.01%; 95% CI, - 0.14 to 0.12). Reductions in FPG from baseline were similar in both groups. At trial completion, 30.6% of patients in the 300 units/mL group and 30.4% of patients in the 100 units/mL group achieved HbA1c <7.0%. The final total daily dosage was 0.92 units/kg/d in the 300 units/mL group and 0.84 units/kg/d in the 100 units/mL group (treatment difference: 11 units/d; 95% CI, 8 to 14). A similar decrease in SMPG was observed in both groups. Patients with ≥ 1 confirmed (≤70 mg/dL) or severe nocturnal hypoglycemic event from wk 9 to 6 mos was 21.6% in the 300 units/mL group vs. 27.9% in the 100 units/mL group (RR: 0.77; 95% CI, 0.61 to 0.99; *P* =.038).
- **Bolli GB, Riddle MC, Bergenstal RM, et al**. ***Diabetes Obes Metab*. 2015;17(4):386-394**. EDITION 3 trial was a multicenter, randomized, open-label, parallel-group, phase 3 trial, in which adult patients with T2DM were randomized (1:1) to once-daily injections of insulin glargine 300 units/mL (n = 435) or insulin glargine 100 units/mL (n = 438) administered in the evening after a 2-wk screening phase. Randomization was stratified by HbA1c (<8.0% and ≥8.0%) and geographic region (non-Japan and Japan) at screening. Inclusion criteria consisted of adult patients (≥18 years of age) with T2DM diagnosis ≥1 y before screening, ≥6 mos OADs, insulin naïve, and HbA1c 7.0% to 10.0%. Metformin and DPP-4 inhibitors could be continued, whereas as all other OADs were discontinued. Insulin doses were initiated at 0.2 units/kg for both groups. Dose adjustments were done weekly, with a 100 to 120 mg/dL fasting SMPG goal and were restricted by protocol. The primary outcome was change in HbA1c after 6 mos. Noninferiority was confirmed if the upper boundary of the two-sided 95% CI was ≤0.4%. At 6 mos, HbA1c was 7.08% in the 300 units/mL group vs. 7.05% in the 100 units/mL group. Noninferiority was demonstrated by the mean change in HbA1c of -1.42% in the 300 units/mL group vs. - 1.46% in the 100 units/mL group (treatment difference: 0.04%; 95% CI, - 0.09 to 0.17). Reductions in FPG from baseline were similar in both groups. At 6 mos, 43.1% of patients in the 300 units/mL group and 42.1% of patients in the 100 units/mL group achieved HbA1c <7.0%. Treatment satisfaction, measured by the Diabetes Treatment Satisfaction Questionnaire, improved in both groups from baseline. Differences in weight gain were not statistically significant. The final total daily dosage was 0.62 units/kg/day in the 300 units/mL group and 0.53 units/kg/day in the 100 units/mL group. A similar decrease in SMPG was observed in both groups. Patients with ≥ 1 confirmed (≤70 mg/dL) or severe nocturnal hypoglycemic events from wk 9 to 6 mos was 16% in the 300 units/mL group vs. 17% in the 100 units/mL group (RR: 0.89; 95% CI, 0.66 to 1.20).

	Brand name (generic name)					
	Levemir (insulin detemir)	**Lantus (insulin glargine)**	**Semglee (insulin glargine-yfgn)**	**Basaglar (insulin glargine)**	**Toujeo (insulin glargine)**	**Tresiba (insulin degludec)**

Insulin degludec (Tresiba) vs. insulin glargine (Lantus) or insulin detemir (Levemir) clinical trials

Note: In all BEGIN trials, noninferiority was achieved if the upper bound of the 95% confidence interval for the difference between treatment groups in change from baseline in HbA1c was ≤ 0.4%. In all trials, hypoglycemia was defined as follows: severe – subject required assistance; confirmed episodes – PG < 56 mg/dL regardless of symptoms or severe episodes; nocturnal confirmed episodes – confirmed episodes occurring between 00:01 h and 05:59 h.

- **BEGIN Basal-Bolus Type 1 trial (glargine). Heller S, Buse J, Fisher M, et al. *Lancet*. 2012;379(9825):1489-1497**. In a 52-wk, multicenter, randomized, open-label, treat-to-target trial, 629 patients with T1DM who had previously used long-term basal-bolus therapy were randomized 3:1 to once-daily insulin degludec or insulin glargine titrated to a target prebreakfast PG value of 70 mg/dL to 90 mg/dL. Insulin aspart was titrated according to a prespecified algorithm. The primary endpoint, mean decrease in HbA1c from baseline to wk 52 was similar between groups. Insulin degludec was noninferior to insulin glargine with an estimated treatment difference of -0.01% (95% CI, -0.14 to 0.12) at wk 52. A similar proportion of patients achieved an HbA1c < 7% (insulin degludec – 40% and insulin glargine – 43%). Mean reductions in FPG and 9-point SMPG profiles were not significantly different between insulin groups, but insulin degludec-treated patients achieved the target SMPG before breakfast of ≤ 90 mg/dL at 5 wks vs. at 10 wks for insulin glargine-treated patients. The overall rate of confirmed hypoglycemic events per PYE was similar (42.54 vs. 40.18 episodes per PYE for insulin degludec and insulin glargine, respectively; *P* = .48); however, the rate of nocturnal hypoglycemic events was significantly lower with insulin degludec than for insulin glargine (4.41 vs. 5.86 episodes per PYE, respectively; rate ratio: 0.75 (95% CI, 0.59 to 0.96)). The rate of severe hypoglycemia events was low and did not differ significantly between insulin groups. Adverse event rates and weight change did not differ between treatment groups.
- **BEGIN Basal-Bolus Type 1 trial (glargine) – 52-week extension**. Bode BW, Buse JB, Fisher M, et al. Diabet Med. 2013;30(11):1293-1297. A total of 351 (74%) and 118 (75%) patients in the insulin degludec and insulin glargine groups entered the 52-wk extension trial. The rate of nocturnal confirmed hypoglycemia was significantly lower with insulin degludec (3.9 vs. 5.3 episodes per PYE for glargine; P = .02), but rates of overall confirmed and severe hypoglycemia were similar between groups. In the extension trial set, the observed reduction in HbA1c, FPG, and SMPG were reduced to a similar extent in both groups with no statistically significant differences.
- **BEGIN Basal-Bolus Type 1 trial (detemir). Davies MJ, Gross JL, Ono Y, et al. Diabetes Obes Metabol. 2014;16(10):922-930.** In a 26-wk, multicenter, randomized, open-label, treat-to-target trial, 455 patients with T1DM who had previously used long-term, basal-bolus therapy were randomized 2:1 to receive treatment with once daily insulin degludec or insulin detemir in addition to premeal insulin aspart. The primary endpoint, the estimated mean change from baseline to wk 26 in HbA1c was 0.73% and 0.65% with degludec and detemir, respectively. The mean estimated treatment difference between groups for HbA1c was -0.09% (95% CI, -0.23 to 0.05; P = .21), which met the a priori definition for noninferiority. At wk 26, mean FPG was significantly lower with degludec (131 mg/dL vs. 161 mg/dL for detemir; P < .0001). Mean 9-point SMPG profiles at wk 26 were similar between degludec and detemir treatment groups except for significantly lower PG at 0:400 h in the detemir group (P = .013). In the detemir group, 32.9% of participants received detemir twice daily due to inadequate glycemic control; this may have partly accounted for the higher dose of basal insulin in the detemir group compared with the degludec group. The overall rate of confirmed hypoglycemia, defined as a plasma glucose <56 mg/dL regardless of symptoms, was similar between treatment groups (45.83 vs. 45.69 episodes per PYE for degludec and detemir, respectively). The rate of nocturnal hypoglycemia, defined as hypoglycemia occurring between 00:01 and 05:59, was significantly less with degludec (4.14 episodes per PYE vs. 5.93 for detemir; P = .0049). The most common adverse events – nasopharyngitis, headache, and hypoglycemia – did not differ between treatment groups.
- **BEGIN Basal-Bolus Type 1 trial (detemir) – 1 y results. Davies M, Sasaki T, Gross JL, et al. *Diabetes Obes Metabol*. 2016;18(1):96-99**. Patients who completed the core 26-wk trial could be enrolled into the 26-wk extension trial, continuing their previous treatment regimen. In the core trial, there were 283 and 138 degludec and detemir completers, respectively and of those, 248 and 122 patients, respectively entered the extension trial. The full safety analysis set included all 455 patients exposed to treatment in the core trial. Similar to 26-wk results, at 52 wks, rates of overall confirmed hypoglycemia (estimated rate ratio of degludec to detemir: 0.95; 95% CI, 0.78 to 1.17) were similar between insulin groups, but the rate of nocturnal confirmed hypoglycemia was significantly lower in the degludec treatment group (estimated rate ratio: 0.67; 95% CI, 0.51 to 0.88). At 52 wks, there was not a significant difference between treatment groups in HbA1c, but degludec treatment was associated with a significantly greater decrease in FPG of 20 mg/dL.

	Brand name (generic name)					
	Levemir (insulin detemir)	Lantus (insulin glargine)	Semglee (insulin glargine-yfgn)	Basaglar (insulin glargine)	Toujeo (insulin glargine)	Tresiba (insulin degludec)

- **BEGIN: Flex T1 trial. Mathieu C, Hollander P, Miranda-Palma B, et al. *J Clin Endocrinol Metab*. 2013;98(3):1154-1162**. In a multicenter, open-label, treat-to-target trial, patients with T1DM who had previously used long-term basal-bolus therapy were randomized 1:1 to receive insulin degludec, administered as a "forced" rotating morning and evening dosing schedule to create alternating short (8-12 h) and long (36-40 h) intervals between injections (forced-flex; n = 164) or as an once-daily dose administered at the evening meal (same time, n = 165), or to receive insulin glargine administered once daily (n = 164) for 26 wks. After 26 wks, patients could enroll in a 26-wk extension trial, in which all degludec-treated patients could administer degludec at any time of the day (free-flex; n = 329) and glargine-treated patients continued the same administration schedule (n = 164). The observed mean change in HbA1c from baseline to wk 26 was similar among treatment groups and the primary objective of the trial, the noninferiority of forced-flex degludec to insulin glargine for change in HbA1c was achieved (estimated treatment difference between forced-flex degludec and insulin glargine: 0.17% (95% CI, 0.04 to 0.30%)). Fasting plasma glucose was reduced to a similar extent in the forced-flex degludec and glargine groups (-23 mg/dL vs. -24 mg/dL, respectively), but was reduced significantly more in the same-time degludec group (-45.8 mg/dL) compared with the forced-flex degludec group. Confirmed and severe hypoglycemia rates were similar across groups at wk 26, but the rate of nocturnal hypoglycemia was significantly lower with forced-flex degludec compared with glargine (estimated rate ratio of degludec to glargine: 0.60; 95% CI, 0.44 to 0.82) and with same-time degludec (estimated rate ratio: 0.63; 95% CI, 0.46 to 0.86). While similar results were seen in the 26-wk extension trial – namely for HbA1c and hypoglycemia outcomes - free-flex degludec was associated with a significant decrease in FPG at week 52 (-31 mg/dL vs. -11 mg/dL for glargine). During the 26-wk extension trial it is unknown how many free-flex degludec participants varied dosing times.
- **BEGIN Basal-Bolus Type 2 trial. Garber AJ, King AB, Del Prato S, et al. *Lancet.* 2012;379(9825):1498-1507**. In a 52-wk, multicenter, randomized, open-label, treat-to-target trial conducted in 992 patients with T2DM +/- use of metformin and/or pioglitazone at baseline, the estimated mean change from baseline to wk 52 in HbA1c was -1.10% with insulin degludec and -1.18% with insulin glargine. Insulin degludec was noninferior to insulin glargine with an estimated treatment difference of 0.08% (95% CI, -0.05 to 0.21%). Mean reductions in FPG and 9-point SMPG profiles were not significantly different between groups. Overall, the rate of hypoglycemia (PG <56 mg/dL or severe episodes requiring assistance) was significantly reduced in the insulin degludec group (11.09 episodes vs. 13.63 episodes per PYE for insulin glargine; estimated rate ratio: 0.82; 95% CI, 0.69 to 0.99; *P* = .0359). While similar proportions of patients experienced at least 1 episode of nocturnal or diurnal hypoglycemia, the rate ratio for nocturnal hypoglycemia (rate ratio: 0.72; 95% CI, 0.51 to 0.99; *P* = .0399) was significantly less with insulin degludec. The rate of severe hypoglycemia was low and similar (0.06 vs. 0.05 episodes per PYE for degludec and glargine, respectively). A similar proportion of patients in each group experienced an adverse event; the most common adverse events in both treatment groups were nasopharyngitis, upper respiratory tract infection, and headache.
- **BEGIN: Flex T2 trial. Meneghini L, Atkin SL, Gough SCL, et al. *Diabetes Care*. 2013;36(4):858-864**. In a multicenter, open-label, treat-to-target trial, 687 patients with T2DM and previously treated with OADs or any basal insulin ± OADs were randomized 1:1:1 to receive insulin degludec, administered as a "forced" rotating morning and evening dosing schedule to create alternating short (8-12 h) and long (36-40 h) intervals between injections (forced-flex) or as an once- daily dose administered at the evening meal (same time), or to receive insulin glargine administered once daily at the same time for 26 wks. The assigned basal insulin was titrated according to a specified algorithm to achieve a prebreakfast target of 70 to <90 mg/dL. In addition to the basal insulin, participants continued prestudy OADs if the dosing and/or frequency of administration remained unchanged. The primary comparison of outcomes was between forced-flex insulin degludec and insulin glargine. Secondarily, forced-flex and same-day insulin degludec groups were compared. For the primary endpoint of observed mean change in HbA1c from baseline to wk 26, forced-flex insulin degludec was noninferior to insulin glargine (estimated mean treatment difference between degludec and glargine: 0.04%; 95% CI, -0.12 to 0.20%). After 26 wks, forced-flex insulin degludec was associated with a significantly greater reduction in FPG than insulin glargine (estimated treatment difference: -0.42 mmol/L; 95% CI, -0.82 to -0.02; *P* = .04). All other assessed endpoints, including mean 9-point SMPG, mean daily insulin dose, and rates of overall and nocturnal hypoglycemia did not differ significantly between forced-flex insulin degludec and insulin glargine. There were no statistically significant differences between forced-flex and same-day insulin degludec for changes from baseline to week 26 in HbA1c, FPG, and mean 9-point SMPG. Rates of confirmed and nocturnal hypoglycemia were also not significantly different between forced-flex and same-day insulin degludec.
- **BEGIN ONCE LONG trial. Rodbard HW, Cariou B, Zinman B, et al. *Diabetes Care.* 2012;35(12):2464-2471**. In a multicenter, open-label, treat-to-target trial, 1,030 insulin-naïve, patients with T2DM treated with OADs were randomized 3:1 to receive once-daily insulin degludec, administered at the evening meal or once-daily insulin glargine, administered at the same time each day. Both insulins were initiated at 10 units and were titrated according to a specified algorithm to achieve a

	Brand name (generic name)					
	Levemir (insulin detemir)	Lantus (insulin glargine)	Semglee (insulin glargine-yfgn)	Basaglar (insulin glargine)	Toujeo (insulin glargine)	Tresiba (insulin degludec)

prebreakfast target of 70 to <90 mg/dL. In addition to the basal insulin, participants could continue OADs if the dosing and/or frequency of administration remained unchanged. From baseline to wk 52, mean HbA1c decreased by 1.06% to 7.1% with insulin degludec and by 1.19% to 7.0% with insulin glargine, meeting the primary objective of the trial to demonstrate the noninferiority of insulin degludec to insulin glargine (estimated treatment difference between degludec and glargine: 0.09%; 95% CI, -0.04 to 0.22%). A similar proportion of patients in each insulin arm achieved an HbA1c <7% and 9-point SMPG profiles decreased similarly in each treatment arm during the trial. Insulin degludec was associated with a statistically significant decrease in FPG compared with insulin glargine with an estimated treatment difference of -0.43 mmol/L between insulin arms (95% CI, -0.74 to -0.13; *P* = .005). In the entire trial period and during the maintenance period (wks 16-52), the proportion and rate of overall confirmed hypoglycemia did not differ significantly between insulin degludec and insulin glargine. While insulin degludec was associated with a significant 36% and 49% relative risk reduction in the rate of confirmed nocturnal hypoglycemia events during the overall and maintenance trial periods, respectively, the rates of nocturnal hypoglycemia rates were low during both time periods (overall: degludec: 0.25 episodes per PYE vs. glargine: 0.39 episodes per PYE; maintenance: degludec: 0.27 episodes per PYE vs. glargine: 0.50 episodes per PYE). Insulin dose, weight gain, and treatment-related adverse events did not differ between treatment groups.

- **BEGIN ONCE LONG trial – 52 wk extension. Rodbard HW, Cariou B, Zinman B, et al. *Diabet Med*. 2013;30(11):1298-1304**. Participants who completed the 52-wk core trial could enter the 52-wk extension trial maintaining prior randomization. Of the 607 participants in the insulin degludec arm, 551 continued into the extension trial and 505 (65%) completed 102 wks. For the insulin glargine arm, the corresponding numbers were 174 and 154 (60%), respectively. Safety and tolerability were the primary endpoints. In extension trial participants, insulin degludec was associated with a significant decrease in the rate of severe hypoglycemic events (0.006 episodes per PYE vs. 0.021 episodes per PYE for glargine; *P* = .042) and nocturnal confirmed hypoglycemic events (0.27 episodes per PYE vs. 0.42 episodes per PYE for glargine; *P* = .002), but not in overall confirmed hypoglycemic events (1.74 episodes per PYE vs. 2.06 episodes per PYE for glargine; *P* = .121) over the entire 104-wk trial period. The rate of adverse events possibly or probably related to treatment, the rate of injection-site reactions, observed mean weight gain, and the rate of major cardiovascular events was not significantly different between treatment groups. In the extension trial set, after 104 wks of treatment, there was not a statistically significant difference in HbA1c (estimated treatment difference: 0.07% (95% CI, -0.07 to 0.22%) between treatment arms, but the reduction in FPG remained statistically greater with insulin degludec.
- **BEGIN LOW VOLUME trial. Gough SCL, Bhargava A, Jain R, et al. *Diabetes Care*. 2013;36(9):2536-2542**. In a multicenter, open-label, treat-to-target trial, 457 insulin-naïve, patients with T2DM treated with OADs were randomized 1:1 to receive once-daily insulin degludec 200 units/mL, administered at the evening meal or once-daily insulin glargine 100 units/mL, administered at the same time each day, both in combination with metformin ± DPP-4. Both insulins were initiated at 10 units and were titrated according to a specified algorithm to achieve a prebreakfast target of <90 mg/dL. Insulin degludec was noninferior to insulin glargine for the primary endpoint of change in HbA1c from baseline to wk 26 with both insulins reducing mean HbA1c by 1.3±1.01% (estimated treatment difference: 0.04; 95% CI, -0.11 to 0.19). A similar proportion of patients in each treatment group achieved target HbA1c levels, target prebreakfast SMPG, and 9-point SMPG profiles were similar. FPG decreased to a significantly greater extent in those treated with insulin degludec (estimated treatment difference: -0.42 mmol/L (95% CI, -0.78 to -0.06). Although the mean daily insulin dose was significantly lower with insulin degludec by 11% (dose ratio: 0.89; 95% CI, 0.82 to 0.98), a similar proportion of patients in each group required >80 units and >160 units. While the number of confirmed overall and confirmed nocturnal hypoglycemia events were numerically greater in the insulin glargine arm, the differences were not significant. The rate of adverse events possibly or probably related to treatment was numerically lower with degludec (0.38 vs. 0.52 events per PYE), but there was no pattern.
- **DEVOTE trial. Marso SP, McGuire DK, Zinman B, et al. *N Engl J Med*. 2017;377(8):723-732**. In a multicenter, double-blind, treat-to-target trial, 7,637 patients with T2DM at high risk for CV events (≥ 50 years old with ≥ 1 co-existing CV or renal condition or ≥ 60 years old with ≥ 1 CV risk factor) and treated with ≥ 1 injectable or oral antihyperglycemic agent were randomized 1:1 to receive insulin degludec or glargine, both added to standard of care and administered once daily in the evening. Patients self-adjusted basal insulin to reach a targeted pre-breakfast PG goal of 71 to 90 mg/dL (or 90 to 126 mg/dL if patient considered vulnerable to hypoglycemia). Bolus insulin aspart was supplied to those continuing or initiating bolus treatment and titrated to a goal preprandial/bedtime PG. The median follow-up time was 1.99 y. The primary outcome, a composite outcome of the first occurrence of death from CV cause, nonfatal MI, or nonfatal stroke, adjudicated by a blinded committee, occurred in 325 (8.5%) and 356 (9.3%) patients in the degludec and glargine groups, respectively (HR: 0.91; 95% CI, 0.78 to 1.06; *P* < .001 for noninferiority). Individual components of the primary outcome did not differ significantly. In a preplanned analysis, the incidence rate of adjudicated events of severe hypoglycemia,

	Brand name (generic name)					
	Levemir (insulin detemir)	**Lantus (insulin glargine)**	**Semglee (insulin glargine-yfgn)**	**Basaglar (insulin glargine)**	**Toujeo (insulin glargine)**	**Tresiba (insulin degludec)**
	defined as an episode requiring the assistance of another person, was significantly lower in the degludec vs. glargine group (3.70 events per 100 patient y vs. 6.25 events per 100 patient years; rate ratio: 0.60; 95% CI, 0.48 to 0.76; *P* < .001 for superiority). The incidence rate of nocturnal hypoglycemia was also significantly lower with degludec (0.65 vs. 1.40 events per 100 patient year for glargine). Post-hoc glycemic control comparisons were similar between treatment groups except for FPG, which was significantly lower in the degludec group (128±56 vs. 136±57 mg/dL for glargine; *P* < .001).					

Abbreviations: ADA = antidrug antibody; BLA = Biologic License Application; CI = confidence interval; CV = cardiovascular; DM = diabetes mellitus; DPP-4 = dipeptidyl peptidase 4; FPG = fasting plasma glucose; HbA1c = hemoglobin A1c; HR = hazard ratio; LA = long acting; MI = myocardial infarction; NDA = New Drug Application; OAD = oral antidiabetic agents; PG = plasma glucose; PYE = patient-years of exposure; RR = risk ratio; SD = standard deviation; SMPG = self-monitored plasma glucose; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus;

Evidence Review

Overview

Historically, insulin products have been approved by the US Food and Drug Administration (FDA) as drugs via new drug applications (NDAs) submitted through section 505 of the Food Drug and Cosmetic Act (FDCA). The Biologics Price Competition and Innovation (BPCI) Act, the legislation that established the biosimilar approval pathway, included a provision that transitioned biological products previously approved as NDAs to biological license applications (BLAs) on March 23, 2020. As a result of the transition, originator insulins, like other biologics, are now subject to biosimilar development.

Prior to the transition, 2 follow-on insulin glargine products (Basaglar and Semglee) were submitted or approved as NDAs pursuant to section 505(b)(2) – an abbreviated new drug approval pathway. Because both were originally submitted as NDAs, they are now considered insulin glargine biologics licensed under separate BLAs. On July 28, 2021, the FDA approved insulin glargine-yfgn (Semglee) as the first interchangeable biologic and the first biosimilar to an insulin product. While non-biosimilar Semglee is currently marketed, it is expected that the interchangeable, biosimilar Semglee will replace the non-biosimilar Semglee as the marketed product in late 2021.

The evidence summary reviews the comparative safety and efficacy data for the FDA-approved long-acting (basal) insulin analogs. At the time of the review, there are 4 separately licensed insulin glargine products (Lantus®, Toujeo®, Basaglar®, non-biosimilar Semglee); separately licensed insulin detemir (Levemir®); separately licensed insulin degludec (Tresiba®); and an interchangeable, biosimilar insulin glargine (Semglee). All insulin analogs have a protracted duration of action, which is achieved through structural modifications of the primary amino acid sequence of human insulin. The prolonged action of insulin glargine is due to formation of slow dissolving microprecipitates after subcutaneous injection while insulins detemir and degludec achieve a protracted duration through self-association and albumin binding after subcutaneous injection.

Insulin glargine versus insulin detemir

Insulins glargine and detemir are full agonists at the insulin receptor; however, insulin detemir binds with 18% less affinity to the insulin receptor due to a fatty acid chain on its primary amino acid sequence.[1] To compensate for the reduction in potency, insulin detemir is formulated at a 4-fold higher concentration per unit relative to glargine (24 versus 6 nmol/unit).[2] The pharmacodynamics (PD) of insulins glargine and detemir were examined in several euglycemic clamp studies. Studies of insulins glargine and detemir consistently demonstrate both insulins have a small peak, which is considerably flatter than the time-action profile of NPH, but not ideally peakless like that of endogenous insulin secretion.[3]

The determination of the comparative duration of action of insulins glargine and detemir from euglycemic clamp studies has been impeded by use of various definitions for duration of action. If a common definition (interval between injection and increase of glucose > 150 mg/dL) is applied across studies, the duration of action of insulin glargine is 22 to 24 hours under single-dose conditions and 24 to 25.6 hours under steady-state conditions.[3] Applying this same definition, the mean duration of action of insulin detemir, dosed at 0.4 units/kg in patients with type 1 diabetes (T1DM) ranged from 21.5 to 23.3 hours in 3 studies.[3,4] A disparate result of 17.5 hours was obtained in a single study employing an insulin detemir dose of 0.35 units/kg, but the result has not been reproduced, suggesting it may be an outlier.[3,5] In comparative studies in patients with type 2 diabetes (T2DM), both insulins glargine and detemir at doses ranging from 0.4 to 1.4 units/kg displayed a mean duration of action of 24 hours.[3,6] Results of the majority of euglycemic studies suggest at doses of 0.4 units/kg and higher, both insulins can be dosed once daily; however, the duration of action of insulin detemir may be shorter than 24 hours in individual patients.

Insulins glargine and detemir have been directly compared in several open-label, randomized, controlled trials (RCT) including 2 comparisons in patients with T1DM and 5 comparisons in patients with T2DM.[7-13] Trials ranged in duration from 24 to 52 weeks. In both T1DM trials and in 3 of the 5 T2DM trials, the dosing algorithms differed between treatment arms.[7-9,11,12] In these 5 trials, insulin glargine was administered once daily in the evening and titrated to achieve a protocol-specified pre-breakfast plasma glucose (PG) target. Insulin detemir was titrated to achieve a protocol-specified pre-breakfast and pre-dinner PG target. [7-9,11,12] With the exception of one trial each in T1DM and T2DM in which insulin detemir was administered twice daily in all patients,[7,12] insulin detemir was initiated once daily with a

second, pre-breakfast dose added if the pre-dinner PG was greater than the protocol-specified target.[8-11,13] Only 2 trials employed equivalent titration schedules.[10,13] In one of these trials, insulins glargine and detemir were administered once daily and titrated to achieve the same target fasting plasma glucose (FPG). In the second trial, insulins glargine and detemir were both titrated to achieve the same pre-breakfast and pre-dinner PG targets, but insulin glargine was administered once daily and insulin detemir was permitted to be administered twice daily if the pre-breakfast PG goal was not achieved.[10]

The glycemic control of insulin detemir was non-inferior to insulin glargine, as assessed by change in glycated hemoglobin (HbA1c) from baseline to trial endpoint (24, 26, or 52 weeks), in both T1DM trials and in 2 of the 4 T2DM trials.[7-10] Insulin detemir was additionally non-inferior to insulin glargine for percentage of patients achieving a HbA1c of less than 7% without symptomatic hypoglycemia.[12] As the majority of trials were biased to favor twice daily dosing in the insulin detemir arm, the finding that insulin detemir was administered twice daily in a high percentage of patients was not unexpected. In trials allowing once or twice daily dosing of insulin detemir, 12.6% to 65.8% of patients completed the trial on a twice-daily regimen.[8-11] While the trials were not designed to compare dosing equivalency, a trend toward higher basal insulin doses was noted in the insulin detemir treatment arms. Across 7 trials, the median percent increase in basal insulin dose in the insulin detemir arms versus the insulin glargine arms was 34% (interquartile range: 14% - 75%) with an increased detemir dose documented in T1DM and T2DM trials.[7-13] After the publication of early trials, the manufacturer claimed that the increased dosing frequency in the insulin detemir arm increased basal insulin doses without improving glycemic control.[8,14] Although increasing the dosing frequency of either glargine or detemir to twice daily appears to increase the daily basal insulin dose of both insulins,[9,10,15,16] results of 2 T2DM trials in which all or a large majority of patients in the detemir treatment arm were dosed once daily failed to confirm the non-inferiority of insulin detemir to insulin glargine.[11,13] These results suggest twice daily dosing of insulin detemir is associated with improved glycemic control. The collective results of comparative trials indicate that some patients treated with insulin detemir may require higher doses and more frequent administration to achieve non-inferior glycemic control to insulin glargine.

Results of observational studies provide additional support for the conclusion that insulins detemir and glargine are not consistently interchangeable on a unit to unit basis in all patients.[17-19] In several observational studies using administrative claims databases, T2DM patients transitioning from insulin glargine to insulin detemir either required higher insulin doses/more frequent insulin administration to maintain glycemic control or experienced poorer glycemic control following the switch.[17-19] Other observational studies in T2DM patients failed to demonstrate statistical differences in doses and/or clinical outcomes between insulins glargine and detemir.[20-23] The inherent limitations of observational studies and the heterogeneity of T2DM likely contribute to disparity in results. Conflicting results of studies support the observation of controlled trials that some patients will achieve similar glycemic control with insulin detemir at the same dose and frequency as insulin glargine while others may require higher, more frequent doses of insulin detemir to achieve comparable glycemic control.

Results of the earliest comparison of insulins glargine and detemir demonstrated insulin detemir was associated with significant decreases in nocturnal and symptomatic nocturnal hypoglycemic events.[7] Subsequent randomized, controlled comparisons failed to demonstrate significant differences between the insulins in the incidence of any, nocturnal, severe, or symptomatic hypoglycemia events.[8-13] Weight gain was numerically lower in the insulin detemir treatment arms as compared with the insulin glargine treatment arms in T1DM trials, but the differences did not reach statistical significance.[7,8] Results of trials conducted in T2DM patients suggest detemir is associated with significantly less weight gain than insulin glargine;[9-13] however, results of one T2DM trial showed the difference was no longer significant in patients receiving insulin detemir twice daily.[9] Of note, the dose of insulin glargine in this trial was lower than in other trials conducted in insulin-naïve patients. Occurrence of adverse events between the insulins were similar with the exception of a higher incidence of skin and injection site reactions in insulin detemir treatment arms, which was likely due to the increased frequency of injections.[9]

The majority of comparative literature evaluated insulins glargine and detemir in the ambulatory setting. It is unknown if the results of these ambulatory studies can be extrapolated to inpatients. There is only 1 published comparison of the 2 insulins in T2DM inpatients.[24] In this

small cross-over study, once-daily insulins glargine and detemir did not differ significantly in the number of days to achieve target FPG or total mean daily insulin dose (bolus and basal).[24] Although these results appear to suggest the insulins are interchangeable on a unit to unit basis in the inpatient setting, enrolled patients had a body mass index of 24 to 25 and had a diagnosis of T2DM for < 5 years, suggesting less advanced stages of T2DM. Also of note, patients receiving insulin glargine first followed by insulin detemir second experienced more hypoglycemia than patients receiving the insulins in the opposite order. A different investigator documented this same phenomenon in an earlier publication.[25]

Insulin degludec versus insulin glargine

Insulin degludec is produced by recombinant DNA technology in *Saccharomyces cerevisiae*.[26] Insulin degludec differs from human insulin by the omission of threonine in the B30 position and by the attachment of a side chain consisting of glutamic acid and a C16 fatty acid. These structural changes cause degludec to form dihexamers in the pharmaceutical formulation and once injected, the dihexamers associate to form arrays of hexamers that precipitate in the subcutaneous tissue. The release of insulin degludec monomers from this depot of multihexamers and to a lesser extent, release of bound insulin degludec from circulating albumin, contributes to the long duration of insulin degludec. After injection of insulin degludec, insulin levels rise gradually, reaching maximal concentration at 10 to 12 hours after injection, after which there is a slow decline with a half-life of 17 to 21 hours. Its ultra-long duration of up to 42 hours is almost twice that of insulin glargine's duration of action.[27]

The approval of insulin degludec was based on the large BEGIN phase 3 development program (phase 3a trials detailed here). For a more detailed description of results, refer to the studies' summaries in the side-by-side comparison. Briefly, the glycemic efficacy of insulin degludec was evaluated in 3 basal-bolus T1DM trials[28-30] and in 7 T2DM trials, 2 of which evaluated a thrice weekly regimen that ultimately Novo Nordisk did not pursue for commercialization and are not included in the evidence summary. Of the remaining 5 T2DM trials, one evaluated insulin degludec as a component of basal-bolus therapy[31] and the remaining 4 evaluated basal-only regimens in combination with different background oral antidiabetic therapy.[32-35]

The trials in the BEGIN program [28-35] were similarly designed. All were open-label, active-controlled, non-inferiority, treat-to-target trials that evaluated the reduction in HbA1c at week 26 or 52 as the primary glycemic endpoint. The prespecified non-inferiority margin for the primary endpoint was 0.4. Once daily insulin glargine 100 units/mL given at the same time every day was the active comparator in most trials.[28,30-35] In the single trial that insulin detemir was the active comparator, insulin detemir was initially dosed once daily, but an additional dose of detemir could be added at the discretion of the investigator after week 8 to optimize glycemic control.[29] In most trials, insulin degludec was given once daily in the evening.[28,31,33-35] Two trials – a single trial each conducted in T1DM and T2DM patients – examined the efficacy of insulin degludec given according to a forced-flex schedule, alternating daily between morning and evening administration to create a short (8 to 12 hours) and a long (36 to 40 hours) dosing interval.[30,32] Insulin degludec was evaluated at a concentration of 200 units/mL in one trial;[34] the remainder of the trials evaluated insulin degludec 100 units/mL.[28,30-33,35] Insulin degludec and the comparator basal insulin were titrated to achieve an aggressive pre-breakfast plasma goal between 70 and 90 mg/dL. In all basal bolus trials, the bolus insulin was dosed to achieved prespecified preprandial and bedtime plasma goals.[28-35]

In addition to the HbA1c endpoint, other key endpoints evaluated in the BEGIN trials included FPG; self-measured plasma glucose (SMPG) profile; episodes of confirmed, nocturnal, and severe hypoglycemia; weight gain; and adverse events. In the BEGIN trials, hypoglycemia was defined as a plasma glucose of less than 56 mg/dL regardless of symptoms. Confirmed hypoglycemic episodes included episodes with a plasma glucose of less than 56 mg/dL or those episodes considered as severe. Severe hypoglycemic episodes were episodes that required assistance and nocturnal episodes were confirmed hypoglycemic episodes that occurred between 12:01 am and 5:59 am.[28-35]

Not unexpectedly, as trials were treat-to-target, once daily insulin degludec was noninferior to once-daily insulin glargine and once- or twice-daily insulin detemir as the upper bound of the 95% confidence interval in all trials was below the prespecified noninferiority margin of 0.4.[28-34] In T1DM trials, excluding forced-flex trials, the point estimate for the treatment difference for HbA1c between insulin degludec and insulin glargine or insulin detemir

slightly favored insulin degludec, suggesting the reduction in HbA1c was numerically greater with insulin degludec.[28,29] In T2DM trials, excluding forced-flex trials, the point estimate for the treatment difference for HbA1c between insulin degludec and insulin glargine favored insulin glargine regardless if insulin degludec was evaluated as a component of a basal bolus regimen or as add-on therapy to oral antidiabetic therapy, suggesting the reduction in HbA1c reduction was numerically greater with insulin glargine.[31,33,34] Forced-flex trials compared outcomes between the different insulin degludec administration strategies and results showed that the glycemic efficacy of variable administration time was non-inferior to once daily, same time administration.[30,32]

Other key glycemic outcomes, including percent of patients achieving the HbA1c goal of < 7% did not differ significantly between insulin degludec and insulin glargine. Fasting plasma glucose was significantly reduced with insulin degludec (vs. insulin glargine) in basal only trials,[32-34] but not in basal bolus trials.[28,29,31] In basal only trials, the mean difference for FPG between insulin degludec and insulin glargine was 7.6 to 7.7 mg/dL.[32-34] Of note, insulin glargine could be dosed in the morning or the evening while insulin degludec was dosed with the evening meal, which may have contributed to differences in FPG because insulin glargine, regardless of administration time, was titrated to achieve an aggressive pre-breakfast goal.

The primary safety assessment evaluated in all the BEGIN trials was hypoglycemia.[28-35] Novo Nordisk hypothesized that degludec's unique PD profile – its relatively stable insulin release and reduced intraindividual variability - would lower the risk of hypoglycemia. Across the BEGIN trials, the definitions for confirmed, severe, and nocturnal hypoglycemia were standardized and a meta-analysis of 7 BEGIN trials was preplanned to assess the superiority of insulin degludec for frequency and rates of hypoglycemic episodes.[36] During the entire trial treatment period (titration and maintenance period), there were no significant differences between insulins degludec and glargine in the T1DM population for overall confirmed, nocturnal confirmed, and severe hypoglycemic episodes.[36] Among the T2DM population, including both insulin-naïve and experienced patients, insulin degludec was associated with a significant decrease in the rate of overall confirmed and nocturnal confirmed hypoglycemic episodes, but not severe episodes. In the subgroup of insulin-naïve T2DM patients, results were similar to the overall T2DM population, but in this subgroup, insulin degludec was also associated with a decreased incidence of nocturnal confirmed hypoglycemic episodes.[36] During its initial review, the FDA questioned the claim that insulin degludec is associated with a lower incidence of hypoglycemia, suggesting that a difference between basal insulins was observed only among the population at lowest risk of hypoglycemia, namely T2DM patients on basal insulin only. The FDA reviewers also suggested that the lower incidence of nocturnal hypoglycemia with insulin degludec was a function of study design rather than a true advantage. The FDA reported that redefining nocturnal hypoglycemia as an episode occurring between midnight and 8:00 am eliminated insulin degludec's superiority. Additionally, forced titration to achieve a pre-breakfast PG goal of 70 to 90 mg/dL likely exacerbated differences in the basal insulins' PD profiles. Other potential adverse events – weight gain, fluid retention, injection site reactions, allergic reactions, and immunogenicity – were similar between insulin degludec and insulin glargine.[37]

Although there was debate about insulin degludec's hypoglycemia superiority, insulin degludec was not approved during its initial review because of a potential cardiovascular safety signal. After receipt of a complete response letter, Novo Nordisk was required to conduct a long-term, comparative cardiovascular safety trial. The DEVOTE trial demonstrated that among patients with T2DM at high risk for cardiovascular events, degludec was non-inferior to glargine for incidence of major cardiovascular events.[38]

Insulin glargine 300 units/mL versus insulin glargine 100 units/mL

Compared to insulin glargine 100 units/mL, insulin glargine 300 units/mL demonstrates less within-day variability in plasma insulin concentration in pharmacokinetic (PK) /PD studies. Additionally, the duration of action of insulin glargine 300 units/mL extends to approximately 30 hours vs. 24 hours for insulin glargine 100 units/mL.[39] Insulin glargine 300 units/mL demonstrated non-inferiority to insulin glargine 100 units/mL in 3 randomized, controlled trials evaluating HbA1c changes in T2DM patients.[40-42] At the completion of all trials, the insulin glargine 300 units/mL group had a slightly greater increase in units of insulin required per day. Investigators theorized this is due to a slight

decrease in bioavailability as the result of a longer subcutaneous residence time with exposure to tissue peptidases.[40-42] Weight gain was similar between the insulin glargine 300 units/mL and 100 units/mL groups. More nocturnal hypoglycemia was observed in the insulin glargine 100 units/mL treatment groups; however, the results were statistically significant in only 2 of the 3 trials.[40-42] Of the 2 trials with statistical significance, the upper bound of the 95% CI was 0.93 and 0.99. Differences in oral antidiabetic medications and adjustment of mealtime insulin, at the discretion of the investigator, may have contributed to this finding.[40,41] Additionally, due to the constraints of the Toujeo pen device, the minimal dosage increase was 3 units, which may have prevented more precise adjustments in the Lantus groups.

Basaglar versus insulin glargine

Basaglar also known as follow-on insulin glargine and insulin glargine (Lantus) share an identical amino acid sequence and are produced by recombinant DNA technology utilizing a non-pathogenic laboratory strain of Escherichia coli.[43] Follow-on insulin glargine is not a biosimilar in the US because follow-on insulin glargine was originally approved via an NDA submitted pursuant to section 505(b)(2) of the FDCA. Section 505(b)(2) is an abbreviated new drug approval pathway that requires full investigations of safety and effectiveness, but allows some of the information for approval to come from sources other than the applicant such as the FDA findings of safety and effectiveness of a previously approved drug (listed drug) or published literature.[44] To justify the use of the FDA's previous findings of safety and effectiveness for insulin glargine, follow-on insulin glargine and insulin glargine were compared in several bridging studies, including an analytical bridging study (identity, purity, potency, stability), a toxicology bridging study, and a pharmacology bridging study. Results of these studies demonstrated the insulins were sufficiently similar to warrant reliance on the FDA's previous findings of safety and effectiveness for insulin glargine for approval of follow-on insulin glargine.[45] Data from insulin glargine's development program in addition to clinical data generated specifically for follow-on insulin glargine provided the evidence for approval of follow-on insulin glargine for use in adults and pediatric patients with T1DM and in adults with T2DM.[43]

The PK and PD of follow-on insulin glargine were compared to EU-approved and US-approved insulin glargine in 2 separate phase 1 euglycemic studies conducted in healthy volunteers.[46] A third euglycemic study was conducted to compare EU-approved and US-approved insulin glargine, the results of which provided scientific justification for use of EU- and US-approved insulin glargine as interchangeable comparators in the pivotal phase 3 trials.[46] The equivalency of PK (area under the curve from time 0 to 24 hours and maximum serum concentration) and PD (maximum glucose infusion rate and total glucose infusion) endpoints was established by demonstrating the 90% confidence interval of the ratios of means of these endpoints fell within 0.80 to 1.25. Point estimates of the ratios (follow on insulin glargine: insulin glargine) ranged from 0.9 to 0.95 for PK endpoints and from 0.91 to 0.99 for PD endpoints.[46] The median duration of action of follow-on insulin glargine and insulin glargine, assessed in patients withT1DM in a 42 hour euglycemic clamp study was similar at 37.1 and 40 hours, respectively.[47]

Two head-to-head phase 3 trials evaluated the comparative glycemic effectiveness of follow-on insulin glargine and insulin glargine.[48,49] Both trials were multinational, multicenter, randomized, treat-to-target trials evaluating adult patients ≥ 18 years of age. The open-label, 52-week ELEMENT-1 trial was conducted in patients with T1DM receiving basal-bolus insulin therapy.[48] The double-blind, 24-week ELEMENT-2 trial was conducted in insulin-naïve and -experienced T2DM patients receiving oral antihyperglycemic drugs (OADs).[49] Results of both trials concluded follow-on insulin glargine was non-inferior to insulin glargine as assessed by change in HbA1c from baseline to week 24. The absolute difference between follow-on insulin glargine and insulin glargine for change in HbA1c at week 24 was 0.108% (95% CI, -0.002% to 0.219%) and 0.052% (95% CI, -0.070% to 0.175%) in the ELEMENT 1 and 2 trials, respectively.[48,49] HbA1c results at 52 weeks in the ELEMENT 1 trial confirmed continued similarity of efficacy between treatment arms.[48] Follow-on insulin glargine achieved non-inferior glycemic control at a similar dose to insulin glargine. In the ELEMENT 1 trial, the mean doses of follow-on insulin glargine and insulin glargine were 0.37 ± 0.01 units/kg/day and 0.36 ± 0.01 units/kg/day, respectively at 24 weeks and 0.38 ± 0.01 units/kg/day and 0.36 ± 0.01 units/kg/day, respectively at 52 weeks.[48] Pre-meal insulin doses were identical

between treatment arms. Likewise, the mean doses of follow-on insulin glargine (0.50 ± 0.03 units/kg/day) and insulin glargine (0.48 ± 0.03 units/kg/day) were similar at week 24 in the ELEMENT 2 trial.[49] There were no significant differences in the proportion of patients achieving HbA1c <7.0% and ≤ 6.5% at weeks 24 and 52 in the ELEMENT 1 trial and at week 24 in the ELEMENT 2 trial.[48,49] SMPG profile was assessed as a secondary efficacy endpoint in both trials. In spite of follow-on insulin glargine demonstrating significantly lower PG values than insulin glargine at bedtime (24- and 52-week assessments) and at 03:00 hours (24-week assessment only) in the ELEMENT 1 trial and at the mid-day pre-meal assessment at week 24 in the ELEMENT 2 trial, there were no significant differences between treatment arms in the incidence or frequency (events per patient per year) of any measured hypoglycemic event (total, severe, or nocturnal events), suggesting differences in SMBG profiles between treatment arms were not clinically meaningful.[48,49]

Additional safety endpoints measured in the phase 3 trials were adverse events, allergic reactions, injection site reactions, weight gain, and immunogenicity. The incidence of adverse events, allergic reactions, and injection site reactions were similar between treatment arms in the ELEMENT 1 and 2 trials.[48,49] There were no significant differences in weight gain between follow-on insulin glargine and insulin glargine. Overall, 40.4% and 39.3% of patients in the follow-on insulin glargine and insulin glargine treatment arms, respectively had detectable antibodies during the 52-week ELEMENT 1 trial (P = .859).[50] Numerically more patients treated with follow-on insulin glargine had detectable antibodies at any point during the 24-week ELEMENT 2 trial than patients treated with insulin glargine (15.3% vs. 11%, respectively; P = .100).[50] This difference was likely attributable to an imbalance at baseline; there were more insulin-experienced patients with detectable antibodies randomized to receive follow-on insulin glargine. Considering only the cohort of insulin-naïve patients at the start of the ELEMENT 2 trial, the proportion of patients developing antibodies were similar between follow-on insulin glargine and insulin glargine treatment arms (12.6% and 12.8%, respectively; P > .999).[50] The incidence of treatment-emergent antibody response (TEAR), an outcome assessing increases in antibody levels due to treatment was similar between treatment groups in T1DM patients at 52 weeks (follow-on insulin glargine: 10.9%; insulin glargine: 9.4%; P = .569) and between treatment groups in T2DM patients at 24 weeks (Both: 3.8%; P > .999).[50] TEAR status had no significant impact on HbA1c, basal insulin dose, or incidence of hypoglycemia.

In the ELEMENT 1 and 2 trials, participants treated with pre-study insulin glargine provided a cohort in which to evaluate the safety and effectiveness of a single transition from insulin glargine to follow-on insulin glargine. Neither trial stratified treatment assignment by pre-study insulin glargine use; therefore, it is important to recognize the cohort was non-randomized. Change in HbA1c from baseline to trial endpoint, achievement of glycemic targets, mean FPG, daily mean PG, basal insulin doses, and incidence of hypoglycemic events were similar between patients transitioning to follow-on insulin glargine and those remaining on insulin glargine.[51] Patients with T1DM transitioning to follow-on insulin glargine experienced a significant difference in percent weight change compared with those remaining on insulin glargine; however, the absolute difference in weight gain was small and most likely a chance finding because the same results were not duplicated in the overall T1DM trial population or in T2DM patients.

MYL-1501D (Semglee) versus insulin glargine

MYL-1501D (insulin glargine-yfgn) is the first approved insulin biosimilar and the first approved interchangeable biosimilar. Although there is a non-biosimilar version of MYL-1501D that was submitted as an NDA pursuant to section 505(b)(2) prior to March 2020 and approved as a BLA in June 2020, this summary will focus on the evidence for approval for biosimilar and interchangeable MYL-1501D – insulin glargine-yfgn – as it is largely expected that interchangeable biosimilar insulin glargine-yfgn will replace non-biosimilar MYL-1501D on the market. Insulin glargine-yfgn was approved under section 351(k) of the Public Health Service Act by demonstrating high similarity to the US reference product, insulin glargine (Lantus) through comparative structural and physicochemical analyses, functional and biological analyses, and nonclinical and clinical analyses. While the FDA considers the totality of evidence for the determination of biosimilarity, the focus of the summary section is clinical data.

In a single-center, randomized, double-blind, 3-way crossover, phase 1 bioequivalence study the PK and PD parameters of MYL-1501D were compared to US

reference insulin glargine (Lantus) and EU reference insulin glargine (Lantus) in patients with T1DM (n = 114).[52] Patients were randomized to receive MYL-1501D, US insulin glargine, or EU insulin glargine as a single subcutaneous dose of 0.4 units/kg on 3 separate visits. Each visit involved a 1 to 6 hour baseline stabilization period to obtain a blood glucose level of 100 mg/dL for at least 1 hour, followed by a 30-hour euglycaemic clamp procedure.[52] The primary PK outcomes were area under the serum insulin glargine concentration-time curve from 0 to 30 hours ($AUC_{ins.0\text{-}30h}$) and maximum serum insulin glargine concentration ($C_{ins.max}$). The primary PD outcomes included area under the glucose infusion rate (GIR)-time curve from 0 to 30 hours ($AUC_{GIR0\text{-}30h}$) and maximum GIR (GIR_{max}).[52] Bioequivalence was demonstrated if the 90% confidence intervals for the primary outcomes was within the lower and upper bounds of 0.80 and 1.25. For each of the PK and PD primary outcomes, the geometric means of ratios between MYL-1501D, US insulin glargine, and EU insulin glargine were close to 1 and the 90% CIs were within the prespecified range.[52]

Two similarly designed parallel studies – a study each in T1DM and T2DM – were conducted to establish the noninferiority of MYL-1501D to reference insulin glargine (Lantus) for glycemic control.[53,54] These studies were submitted in support of the original BLA. Both trials were multinational, multicenter, randomized, treat-to-target trials evaluating adult patients. The open-label, 52-week INSTRIDE 1 trial was conducted in patients with T1DM receiving basal-bolus therapy.[53] The open-label, 26-week INSTRIDE 2 trial was conducted in insulin-naive and -experienced patients with T2DM receiving oral antihyperglycemic drugs.[54] Results of both trials demonstrated that MYL-1501D was non-inferior – based on a non-inferiority margin of 0.4 – to insulin glargine as assessed by change in HbA1c from baseline to week 24. The absolute difference between MYL-1501D and insulin glargine for change in HbA1c at week 24 was 0.03% (95% CI, -0.066 to 0.117%) and 0.06% (95% CI, -0.10 to 0.22%) in the INSTRIDE 1 and 2 trials, respectively.[53,54] In addition to MYL-1501D being non-inferior to insulin glargine for change in HbA1c, results demonstrated no differences between treatment groups for other endpoints including change in FPG, change in SMPG, weight gain, incidence of hypoglycemia, and basal insulin dose.

To be designated as an interchangeable biosimilar, data was submitted to show MYL-1501D produces the same clinical results if the patient is alternated between the biosimilar and the reference product as compared to remaining on the reference product. The INSTRIDE 3 trial enrolled and randomized patients who completed 52 weeks of treatment in the INSTRIDE 1 trial to receive an additional 36 weeks of treatment with reference insulin glargine (non-switching arm) or with MYL-1501D and reference insulin glargine, alternating between products every 12 weeks (switching arm).[55] After 36 weeks, the switching arm was equivalent (±0.4%) to the non-switching arm for change in HbA1c from baseline to week 36. Although there were numerical differences in insulin doses between the switching arm during MYL-1501D treatment periods (weeks 0 to 4 and weeks 24 to 36) and the non-switching arm, early differences were attributable to baseline differences in basal insulin dose and late differences were not determined to be clinically meaningful. Nocturnal hypoglycemia occurred more frequently in the switching arm, but this trend was seen during all treatment periods, including the period with reference insulin glargine, suggesting an imbalance between groups in hypoglycemia risk factors rather than an imbalance due to insulin product.[55]

The immunogenicity of MYL-1501D and reference insulin glargine were evaluated in INSTRIDE 1 (n = 558) and INSTRIDE 2 (n = 560) studies.[56] Immunogenicity analyses were conducted in the safety population of each study, which included all patients who received at least 1 dose of study drug. The incidence rates and change from baseline in levels of antidrug antibodies (ADA) and anti-host cell protein (anti-HCP) antibodies were measured by radioimmunoprecipitation assay and a bridging immunoassay, respectively. Blood samples for immunogenicity assessment were collected at baseline and weeks 2, 4, 12, and 24 in both studies, and additionally at weeks 36 and 52 for INSTRIDE 1. The results of INSTRIDE 1 were analyzed using mixed-effects model and the results of INSTRIDE 2 were analyzed with a nonparametric Wilcoxon rank sum test. Using the MYL-1501D assay and reference insulin glargine assay, there were no statistically significant changes from baseline in total or cross-reactive ADA percent binding. In INSTRIDE 1 and INSTRIDE 2, total or cross-reactive ADA-positive responses were similar between the treatment groups at all time points. In both studies, there were no statistically significant differences between the two groups in change from baseline anti-HCP antibodies.[56]

As the first approved interchangeable biosimilar to insulin glargine, insulin glargine-yfgn will have 12 months of market exclusivity from the date of initial marketing. If another biosimilar version of insulin glargine is approved during this 12-month window, it will not be eligible to receive an interchangeability designation until the interchangeability exclusivity of insulin glargine-yfgn expires. While the FDA states that biosimilars designated as interchangeable can be substituted for the originator reference product without notification of the prescriber, state boards govern dispensing rules and pharmacists must be aware of state-specific requirements for biosimilar substitution (e.g., physician notification, patient notification, record retention, etc).

Summary/Conclusions

Alteration of the amino acid sequence of human insulin by recombinant DNA technology has led to the development of several insulin analogs with protracted durations of action. These include insulins glargine, detemir, and degludec. The FDA approved the first follow-on insulin analog in December 2015 and the first interchangeable biosimilar insulin analog in July 2021.

There are multiple published comparisons of insulins glargine and detemir. While results of the majority of controlled comparisons suggest both insulins produce similar reductions in HbA1c in T1DM and T2DM, the optimal dose and frequency of insulin detemir to achieve similar glycemic control is controversial. In most controlled studies, patients treated with insulin detemir required higher doses and twice-daily administration. Many attribute the differences in doses and frequency between the insulins to flawed study designs; however, a growing body of evidence in the heterogeneous T2DM population supports the contention that the 2 insulins are not reliably interchangeable on a unit to unit basis or at the same dosing frequency. Considered together, results of controlled and observational data indicate someT2DM patients may require higher doses and/or more frequent administration with insulin detemir than with insulin glargine to achieve comparable glycemic control. Whether or not the same is true in the more homogenous T1DM population is unknown as there is a paucity of observational data comparing the insulins in this population. At similar levels of glycemic control, insulins glargine and detemir have a comparable incidence of hypoglycemia. Insulin detemir is associated with less weight gain than insulin glargine, although it may lose some of its benefit if dosed twice daily. As all comparisons of insulins detemir and glargine with the exception of 1 were conducted in outpatients, it is unknown if results can be extrapolated to the acute setting.

Insulin degludec effectively lowers glucose levels among T1DM and T2DM patients to a similar extent as insulin glargine. Due to its ultra-long half-life, insulin degludec is the first insulin that can be administered at variable times day to day without reducing glycemic efficacy. This may be an advantage among patients who need greater flexibility in dosing interval. Its ultra-long half-life may also be an advantage for patients unable to achieve glycemic control with once daily insulin glargine 100 units/mL, although insulin glargine 300 units/mL with its longer half-life may remove this potential differentiator. While insulin degludec's flatter insulin curve and lower variability may reduce nocturnal hypoglycemia, in clinical trials this advantage was limited to insulin naïve T2DM patients who were treated with basal insulin only and titrated to an aggressive pre-breakfast plasma glucose goal. It is unclear if insulin degludec is superior to other insulin basal analogs for incidence of hypoglycemia in other patient populations and/or at different glycemic goals.

Follow-on insulin glargine (Basaglar) and insulin glargine-yfgn have an identical amino acid sequence to reference insulin glargine (Lantus); however, Basaglar is licensed as a separate biologic and insulin glargine-yfgn, which was initially licensed as a separate biologic, is now licensed as the first and only interchangeable insulin biosimilar because it was approved after insulins were transitioned from drugs to biologics in March 2020 per the BPCI Act. Though follow-on insulin glargine and insulin glargine-yfgn were approved through different pathways, both were approved based on an abbreviated approval processes that relied on the safety and effectiveness of reference insulin glargine. Results of comparative clinical research suggest that follow-on insulin glargine and insulin glargine-yfgn are pharmacokinetically and pharmacodynamically equivalent to insulin glargine in healthy subjects and are non-inferior to insulin glargine for reduction in HbA1c in adult patients with T1DM and T2DM on a unit-to-unit basis. Weight gain, immunogenicity, hypoglycemia, and adverse events are similar between follow-on insulin glargine and insulin glargine and insulin glargine-yfgn and insulin glargine.

While there may be subtle differences in duration, hypoglycemia occurrence, insulin dose, and weight gain among the basal insulin analogs, in outpatient practice, the choice among insulin analogs is likely to be more influenced by cost and insurance coverage than differences among insulins. For inpatient practice, dosage form in addition to cost may influence formulary decisions. All insulin analogs are available as multi-dose vials except for follow-on insulin glargine (Basaglar), which is only supplied as a single patient prefilled pen.

References

1. Swinnen S, DeVries JH. Higher dose requirements with insulin detemir in type 2 diabetes – Three cases and review of the literature. Diabetes Res Clin Pract. 2009;84:e24-e26.
2. Owens DR, Matfin G, Monnier L. Basal insulin analogues in the management of diabetes mellitus: What progress have we made? Diabetes Metab Res Rev. 2014;30(2):104-119.
3. Heise T and Pieber TR. Towards peakless, reproducible and long-acting insulins. An assessment of the basal analogues based on isoglycaemic clamp studies. Diabetes, Obesity and Metabolism. 2007;9:648-659.
4. Koehler G, Treiber G, Wutte A et al. Pharmacodynamics of the long-acting insulin analogues detemir and glargine following single-doses and under steady-state conditions in patients with type 1 diabetes. Diabetes Obes Metab. 2014;16(1):57-62.
5. Porcellati F, Rossetti P, Busciantella NR et al. Comparison of pharmacokinetics and dynamics of the long-acting insulin analogs glargine and detemir at steady state in type 1 diabetes: a double-blind, randomized, crossover study. Diabetes Care. 2007;30(10):2447-2452.
6. Luzio SD, Dunseath GJ, Atkinson MD, Owens DR. A comparison of the pharmacodynamics profiles of insulin detemir and insulin glargine: a single dose clamp study in people with type 2 diabetes. Diabetes Metab. 2013;39(6):537-542.
7. Pieber TR, Treichel HC, Hompesch B et al. Comparison of insulin detemir and insulin glargine in subjects with type 1 diabetes using intensive insulin therapy. Diabet Med. 2007;24(6):635-642.
8. Heller S, Koenen C, Bode B. Comparison of insulin detemir and insulin glargine in a basal-bolus regimen, with insulin aspart as the mealtime insulin, in patients with type 1 diabetes: a 52-week, multinational, randomized, open-label, parallel-group, treat-to-target noninferiority trial. Clin Ther. 2009;31(10):2086-2097.
9. Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Schernthaner G. A randomized, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naïve people with type 2 diabetes. Diabetologia. 2008;51(3):408-416.
10. Hollander P, Cooper J, Bregnhoj J, Pedersen CB. A 52-week, multinational, open-label, parallel group, noninferiority, treat-to-target trial comparing insulin detemir with insulin glargine in a basal-bolus regimen with mealtime insulin aspart in patients with type 2 diabetes. Clin Ther. 2008;30(11):1976-1987.
11. Raskin P, Gylvin T, Weng W, Chaykin L. Comparison on insulin detemir and insulin glargine using a basal-bolus regimen in a randomized, controlled clinical study in patients with type 2 diabetes. Diabetes Metab Res Rev. 2009;25(6):542-548.
12. Swinnen SG, Dain MP, Aronson R et al. A 24-week, randomized, treat-to-target trial comparing initiation of insulin glargine once-daily with insulin detemir twice-daily in patients with type 2 diabetes inadequately controlled on oral glucose-lowering drugs. Diabetes Care. 2010;33(6):1176-1178.
13. Meneghini L, Kesavadev J, Demissie M, Nazeri A, Hollander P. Once-daily initiation of basal insulin as add-on to metformin: a 26-week, randomized, treat-to-target trial comparing insulin detemir with insulin glargine in patients with type 2 diabetes. Diabetes Obes Metab. 2013;15(8):729-736.
14. Le Floch JP, Levy M, Mosnier-Pudar H for the Assessment of Detemir Administration in Progressive Treat-to-Target Trial (ADAPT) Study Group. Comparison of once-versus twice-daily administration of insulin detemir, used with mealtime insulin aspart, in basal-bolus therapy for type 1 diabetes: assessment of detemir administration in a progressive treat-to-target trial (ADAPT). Diabetes Care. 2009;32(1):32-37.
15. Albright ES, Desmond R, Bell DS. Efficacy of conversion from bedtime NPH insulin injection to once- or twice-daily injections of insulin glargine in type 1 diabetics patients using basal/bolus therapy [letter]. Diabetes Care. 2004;27:632-633.
16. Garg SK, Gottlieb PA, Hisatomi ME, et al. Improved glycemic control without an increase in severe hypoglycemia episodes in intensively treated patients with type 1 diabetes receiving morning, evening, or split dose insulin glargine. Diabetes Res Clin Pract. 2004;66:49-56.
17. Bryant GA, McDanel DL, Horner KE, Farris KB, Newkirk EN. Evaluation of dosing and clinical outcomes in patients undergoing conversion of insulin glargine to insulin detemir. Pharmacotherapy. 2013;33(1):56-62.
18. Wei W, Zhou S, Miao R et al. Much ado about nothing? A real-world study of patients with type 2 diabetes switching basal insulin analogs. Adv Ther. 2014;31(5):539-560.
19. Levin P, Wei W, Miao R et al. Therapeutically interchangeable? A study of real-world outcomes associated with switching basal insulin analogues among US patients with type 2 diabetes mellitus using electronic medical records data. Diabetes Obes Metab. 2015;17(3):245-253.
20. Verges B, Brun JM, Tawil C, Alexandre B, Kerlan V. Strategies for insulin initiation: insights from the FRENCH LIGHT observational study. Diabetes Metab Res Rev. 2012;28(1):97-105.
21. Yenigun M, Honka M. Switching patients from insulin glargine-based basal-bolus regimens to a once daily insulin-detemir-based basal-bolus regimen: results from a subgroup of the PREDICTIVE study. Int J Clin Pract. 2009;63(3):425-432.
22. Borah BJ, Darkow T, Bouchard J, Aagren M, Forma F, Alemayehu B. A comparison of insulin use, glycemic control, and health care costs with insulin detemir and insulin glargine in insulin-naïve patients with type 2 diabetes. Clin Ther. 2009;31(3):623-631.
23. Jakobsen M, Dalsgaard M, Hormann M, Moller DV. Insulin analogues dosing and costs – comparing real-life daily doses of insulin detemir and insulin glargine in type 2 diabetes patients. BMC Endocr Disord. 2012;12:21.
24. Zhang T, Lin M, Li W et al. Comparison of the efficacy and safety of insulin detemir and insulin glargine in hospitalized patients with type 2 diabetes: A randomized crossover trial. Adv Ther. 2016;33(2): 178-185.
25. Kabadi UM. Deleterious outcomes after abrupt transition from insulin glargine to insulin detemir in patients with type 1 diabetes mellitus. Clin Drug Investig. 2008;28(11):697-701.
26. Tresiba [package insert]. Plainsboro, NJ: Novo Nordisk;2019.
27. Rendell M. United States experience of insulin degludec alone or in combination for type 1 and type 2 diabetes. *Drug Des Devel Ther*. 2017;11:1209-1220.
28. Heller S, Buse J, Fisher M, et al for BEGIN Basal-Bolus Type 1 trial investigators. Insulin degludec, an ultra-long acting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomized, open-label, treat-to-target non-inferiority trial. *Lancet*. 2012;379(9825):1489-1497.

29. Davies MJ, Gross JL, Sasaki T, et al for the BEGIN BB T1 Study Group. Efficacy and safety of insulin degludec given as part of basal-bolus treatment with mealtime insulin aspart in type 1 diabetes: a 26-week randomized, open-label, treat-to-target non-inferiority trial. *Diabetes Obes Metab*. 2014;16(10):922-930.
30. Mathieu C, Hollander P, Miranda-Palma B, et al for the BEGIN: Flex T1 trial investigators. Efficacy and safety of insulin degludec in a flexible dosing regimen vs. insulin glargine in patients with type 1 diabetes (BEGIN: Flex T1): a 26-week randomized, treat-to-target trial with a 26-week extension. *J Clin Endocrinol Metab*. 2013;98(3):1154-1162.
31. Garber AJ, King AB, Del Prato S, et al for the BEGIN BB T2D trial investigators. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes (BEGIN Basal-Bolus Type 2): a phase 3, randomized, open-label, treat-to-target non-inferiority trial. *Lancet*. 2012;379(9825):1498-1507.
32. Meneghini L, Atkin SL, Gough SCL, et al for the BEGIN FLEX trial investigators. The efficacy and safety of insulin degludec given in variable once-daily dosing intervals compared with insulin glargine and insulin degludec dosed at the same time daily: a 26-week, randomized, open-label, parallel-group, treat-to-target trial in individuals with type 2 diabetes. *Diabetes Care*. 2013;36(4):858-864.
33. Zinman B, Philis-Tsimikas, Cariou B, et al for BEGIN Once Long trial investigators. Insulin degludec versus insulin glargine in insulin-naïve patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). *Diabetes Care*. 2012;35(12):2464-2471.
34. Gough SCL, Bhargava A, Jain R, Mersebach H, Rasmussen S, Bergenstal RM. Low-volume insulin degludec 200 units/ml once daily improves glycemic control similarly to insulin glargine with a low risk of hypoglycemia in insulin-naïve patients with type 2 diabetes: a 26-week, randomized, controlled, multinational, treat-to-target trial: the BEGIN LOW VOLUME trial. *Diabetes Care*. 2013;36(9):2536-2542.
35. Onishi Y, Iwamoto Y, Yoo SJ, Clauson P, Tamer SC, Park S. Insulin degludec compared with insulin glargine in insulin-naïve patients with type 2 diabetes: a 26-week, randomized, controlled, Pan-Asian, treat-to-target trial. *J Diabetes Invest*. 2013;4:605-612.
36. Ratner RE, Gough SCL, Mathieu C, et al. Hypoglycaemia risk with insulin degludec compared with insulin glargine in type 2 and type 1 diabetes: a pre-planned meta-analysis of phase 3 trials. *Diabetes Obes Metab*. 2013;15(2):175-184.
37. Center for Drug Evaluation and Research. Application Number: 203313Orig1s000, 203314Orig1s000. Summary Review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/203313orig1s000_203314orig1s000sumr.pdf. Accessed October 13, 2021.
38. Marso SP, McGuire DK, Zinman B, et al for DEVOTE study group. Efficacy and safety of degludec versus glargine in type 2 diabetes. *N Engl J Med*. 2017;377(8):723-732.
39. Owens DR, S Bailey T, Fanelli CG, Yale JF, Bolli GB. Clinical relevance of pharmacokinetic and pharmacodynamic profiles of insulin degludec (100, 200 U/mL) and insulin glargine (100, 300 U/mL) - a review of evidence and clinical interpretation. *Diabetes Metab*. 2019;45(4):330-340.
40. Riddle MC, Bolli GB, Ziemen M, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using basal and mealtime insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 1). *Diabetes Care*. 2014; 37(10):2755-2762.
41. Yki-Järvinen H, Bergenstal R, Ziemen M, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 2 diabetes using oral agents and basal insulin: glucose control and hypoglycemia in a 6-month randomized controlled trial (EDITION 2). *Diabetes Care.* 2014.;37(12):3235-43.
42. Bolli GB, Riddle MC, Bergenstal RM, et al. New insulin glargine 300 U/ml compared with glargine 100 U/ml in insulin-naïve people with type 2 diabetes on oral glucose-lowering drugs: a randomized controlled trial (EDITION 3). *Diabetes Obes Metab*. 2015;17(4):386-394.
43. Basaglar [package insert]. Indianapolis, IN: Eli Lilly and Company; 2021.
44. U.S. Department of Health and Human Services, Food and Drug Administration, and Center for Drug Evaluation and Research. Applications covered by section 505(b)(2). http://www.fda.gov/downloads/Drugs/.../Guidances/ucm079345.pdf. Accessed December 1, 2016.
45. Center for Drug Evaluation and Research. Application number: 205692Orig1s000. Summary review. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/205692Orig1s000SumR.pdf. Accessed November 23, 2016.
46. Linnebjerg H, Lam EC, Seger ME. Comparison of the pharmacokinetics and pharmacodynamics of LY2963016 insulin glargine and EU- and US-approved versions of Lantus insulin glargine in healthy subjects: Three randomized euglycemic clamp studies. Diabetes Care. 2015;38(12):2226-2233.
47. Linnebjerg H, Lam EC, Zhang X et al. Duration of action of two insulin glargine products, LY29630169 insulin glargine and Lantus insulin glargine, in subjects with type 1 diabetes mellitus. Diabetes Obes Metab. 2017;19(1):33-39.
48. Blevins TC, Dahl D, Rosenstock J et al. Efficacy and safety of LY2963016 insulin glargine compared with insulin glargine (Lantus) in patients with type 1 diabetes in a randomized controlled trial: the ELEMENT1 study. Diabetes Obes Metab. 2015;17(8):726-733.
49. Rosenstock J, Hollander P, Bhargava A et al. Similar efficacy and safety of LY2963016 insulin glargine and insulin glargine (Lantus) in patients with type 2 diabetes who were insulin-naïve or previously treatment with insulin glargine: a randomized, double-blind controlled trial (the ELEMENT 2 study). Diabetes Obes Metab. 2015;17(8):734-741.
50. Ilag LL, Deeg MA, Costigan T et al. Evaluation of immunogenicity of LY2963016 insulin glargine compared with Lantus insulin glargine in patients with type 1 or type 2 diabetes mellitus. Diabetes Obes Metab. 2016;18(2):159-168
51. Hadjiyianni L, Dahl D, Lacaya LB, Pollom RK, Chang CL, Ilag LL. Efficacy and safety of LY2963016 insulin glargine in patients with type 1 and type 2 diabetes previously treated with insulin glargine. Diabetes Obes Metab. 2016;18(4):425-429.
52. Heise T, Donnelly C, Barve A, Aubonnet P. Pharmacokinetic and pharmacodynamic bioequivalence of proposed biosimilar MYL-1501D with US and European insulin glargine formulations in patients with type 1 diabetes mellitus. *Diabetes Obes Metab*. 2020 Apr;22(4):521-529.
53. Blevins TC, Barve A, Sun B, Ankersen M. Efficacy and safety of MYL-1501D vs. insulin glargine in patients with type 1 diabetes after 52 weeks: Results of the INSTRIDE 1 phase III study. *Diabetes Obes Metab*. 2018;20(8):1944-1950.
54. Blevins TC, Barve A, Sun B, et al. Efficacy and safety of MYL-1501D versus insulin glargine in patients with type 2 diabetes after 24 weeks: Results of the phase III INSTRIDE 2 study. *Diabetes Obes Metab*. 2019;21(1):129-135.
55. Blevins TC, Barve A, Raiter Y, et al. Efficacy and safety of MYL-1501D versus insulin glargine in people with type 1 diabetes mellitus: Results of the INSTRIDE 3 phase 3 switch study. *Diabetes Obes Metab.* 2020;22(3):365-372.
56. Sun B, Sengupta N, Rao A, et al. Similar immunogenicity profiles between the proposed biosimilar MYL-1501D and reference insulin glargine in patients with diabetes mellitus: the phase 3 INSTRIDE 1 and INSTRIDE 2 studies. *BMC Endocr Disord*. 2021;21(1):129.

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