A New Basal Insulin Option:
The BEGIN Trials in Patients With Type 2 Diabetes

Reviewed by Dawn Battise, PharmD

STUDIES

Initiating insulin degludec (study A): Zinman B, Philis-Tsimikas A, Cariou B, Handelsman Y, Rodbard HW, Johansen T, Endahl L, Mathieu C, on behalf of the NN1250-3579 (BEGIN Once Long) Trial Investigators: Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial. *Diabetes Care* 35:2464–2471, 2012.

Insulin degludec as basal-bolus therapy (study B): Garber AJ, King AB, Del Prato S, Sreenan S, Balci MK, Muńoz-Torres M, Rosenstock J, Endahl LA, Ocampo Francisco AM, Hollander P, on behalf of the NN1250-3582 (BEGIN Basal-Bolus Type 2) Trial Investigators: Insulin degludec, an ultra-long-acting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 2 diabetes: a phase 3, randomized, open-label, treat-to-target noninferiority trial. *Lancet* 379:1498–1507, 2012.

SUMMARY

Objectives. To evaluate, in adults with type 2 diabetes, the safety and efficacy of insulin degludec compared to insulin glargine *A*) in insulin-naive patients and *B*) as intensified basal-bolus therapy.

Design and methods. Study A: Adults with type 2 diabetes inadequately controlled with oral glucose-lowering agents were randomized to insulin degludec (*n* = 773) or insulin glargine (*n* = 257) once daily, both in combination with metformin. Insulin was titrated to achieve a breakfast fasting plasma glucose (FPG) level of 70–90 mg/dl. The primary efficacy endpoint was noninferiority of insulin degludec to insulin glargine in A1C reduction (≤ 0.4%) after 52 weeks.

Study B: Adults with type 2 diabetes inadequately controlled with insulin ± oral agents were randomized to insulin degludec (*n* = 755) or insulin glargine (*n* = 251) once daily in combination with insulin aspart before meals with or without metformin and/or pioglitazone. Insulin was titrated to achieve a breakfast FPG level of 70–90 mg/dl. The primary efficacy endpoint was noninferiority of insulin degludec to insulin glargine in A1C reduction (≤ 0.4%) after 52 weeks.

Results. Study A: After 52 weeks of treatment, insulin degludec and insulin glargine decreased mean A1C concentrations from baseline by 1.06 and 1.19%, respectively (Table 1). An estimated treatment difference of 0.09% (95% CI –0.04 to 0.22%) indicated that insulin degludec was noninferior to insulin glargine. Among those in the safety analysis set, rates of overall hypoglycemia were similar (1.52 vs. 1.85 events/patient-year of exposure [PYE], respec-

tively), whereas nocturnal hypoglycemia was significantly less frequent with insulin degludec (0.25 vs. 0.39 events/PYE, respectively, *P* = 0.038), particularly during the maintenance period (weeks 16–52). Rates of severe hypoglycemia were low and occurred significantly less frequently with insulin degludec (0.003 vs. 0.023 episodes/PYE, respectively, *P* = 0.017) (Table 2). Adverse event rates were otherwise similar.

Study B: After 52 weeks of treatment, insulin degludec and insulin glargine decreased mean A1C concentrations from baseline by 1.10 and 1.18%, respectively (Table 1). An estimated treatment difference of 0.08% (95% CI –0.05 to 0.21%) indicated that insulin degludec was noninferior to insulin glargine. Among those in the safety analysis set, rates of overall hypoglycemia were lower in those treated with insulin degludec (11.09 vs. 13.63 episodes/PYE, *P* = 0.0359). In addition, rates of diurnal (9.28 vs. 11.39 episodes/PYE, *P* = 0.044) and nocturnal (1.39 vs. 1.84 episodes/PYE, *P* = 0.0399) hypoglycemia were significantly lower in the insulin degludec group. Rates of severe hypoglycemia were similar between groups (0.06 and 0.05 episodes/PYE, respectively)

Table 1. Comparison of Mean A1C Concentration Reductions (%)		
	Insulin Degludec	**Insulin Glargine**
Study A	1.06	1.19
Study B	1.10	1.18

Table 2. Comparison of Hypoglycemic Events/PYE	Insulin Degludec	Insulin Glargine
Study A		
Overall	1.52	1.85
Nocturnal*	0.25	0.39
Severe	0.003	0.023
Study B		
Overall†	11.09	13.63
Diurnal‡	9.28	11.39
Nocturnal§	1.39	1.84
Severe	0.06	0.05

*P = 0.038
†P = 0.0359
‡P = 0.044
§P = 0.0399

(Table 2). Rates of other adverse events did not differ between groups.

Conclusion. As initial or basal-bolus insulin therapy, insulin degludec is noninferior to insulin glargine in reducing A1C concentrations over 52 weeks. Rates of nocturnal hypoglycemia are significantly lower with insulin degludec than with insulin glargine.

COMMENTARY
Data from the U.K. Prospective Diabetes Study confirmed that many patients with type 2 diabetes will eventually require insulin therapy.[1] However, insulin use is known to increase the risk of hypoglycemia, and evidence shows that fear of hypoglycemia can contribute to worse glycemic control.[1,2] An ideal basal insulin will provide peakless glucose-lowering activity for at least 24 hours with minimal variability and will minimize the risk of adverse effects including hypoglycemia.

Insulin degludec is an ultra-long-acting insulin that is under review by the U.S. Food and Drug Administration (FDA). This novel formulation forms a multihexamer upon subcutaneous injection that dissociates into monomers, which are absorbed at a constant rate.[3] The two studies reviewed demonstrate that insulin degludec is noninferior to insulin glargine in terms of A1C reduction and also offers potentially lower rates of hypoglycemia.

Additional Study Results
In Study A, results demonstrated that, as expected with a treat-to-target design, degludec was noninferior to glargine in terms of A1C reduction. In addition, during the last 12 weeks of treatment, similar proportions treated with degludec and glargine achieved an A1C level of < 7% without hypoglycemia (42 and 46%, respectively, P = 0.34) and without nocturnal hypoglycemia (53 and 54%, respectively, P = 0.68).

However, a significantly greater reduction in FPG was observed with degludec than with glargine (–68 vs. –59 mg/dl, P = 0.005). This was achieved with similar daily insulin doses (0.59 units/kg for degludec and 0.60 units/kg for glargine at the end of the study).

Rates of overall hypoglycemia were similar throughout the study (P = 0.106) and during the maintenance phase (P = 0.067). However, nocturnal hypoglycemia was 36% lower with degludec (P = 0.038) across the study, increasing to 49% during the maintenance phase (P = 0.004). Additionally, severe hypoglycemia events were significantly lower with degludec (P = 0.017), although few events were reported for either group.

Using the short-form health survey, version 2.0 (SF-36), researchers observed significant improvement in the "overall physical" (P = 0.33) and "physical functioning" (P = 0.016) categories, both in favor of degludec. Mean weight gain was similar (2.4 vs. 2.1 kg, respectively, for insulin degludec and insulin glargine).

In Study B, results demonstrated that degludec was noninferior to glargine, both in combination with insulin aspart with or without metformin and/or pioglitazone, in reduction of A1C. Similar proportions of those treated with degludec and glargine achieved an A1C < 7% (49 and 50% of subjects, respectively). The decrease in FPG was also similar (–41 vs. –36 mg/dl, respectively). At 52 weeks, the total daily dose of basal insulin was slightly greater and of bolus insulin was slightly lower in the degludec group.

In contrast to Study A, rates of overall hypoglycemia were significantly lower with degludec throughout the study but, according to post-hoc analysis, were similar during the maintenance period from weeks 16 to 52 (rate ratio 0.82, P = 0.06). Rates of nocturnal hypoglycemia were significantly lower with degludec over the 52 weeks (P = 0.0399) and during the maintenance period (rate ratio 0.72, P = 0.0493). Severe hypoglycemic reactions could not be evaluated because too few events occurred.

Table 3. Study A: Select Baseline Characteristics

	Insulin Degludec	Insulin Glargine
Participants randomized (full analysis set)	773	257
Participants exposed to treatment (safety analysis set)	766 (99.1)	257 (100)
Female	302 (39.1)	90 (35.0)
Race		
White	680 (88.0)	231 (89.9)
Black	57 (7.4)	16 (6.2)
Asian	18 (2.3)	3 (1.2)
Other	18 (2.3)	7 (2.7)
Ethnicity: Hispanic or Latin American	129 (16.7)	48 (18.7)
Age (years)	59.3 ± 9.7	58.7 ± 9.9
Body weight (kg)	89.4 ± 17.7	91.8 ± 15.8
BMI (kg/m^2)	30.9 ± 4.8	31.6 ± 4.4
Duration of diabetes (years)	9.4 ± 6.3	8.6 ± 5.7
A1C (%)	8.2 ± 0.8	8.2 ± 0.8
Systolic blood pressure (mmHg)	133.8 ± 15.2	133.8 ± 15.1
Diastolic blood pressure (mmHg)	79.7 ± 8.7	79.8 ± 8.5
HDL cholesterol (mmol/l)	1.15 ± 0.33	1.12 ± 0.28
LDL cholesterol (mmol/l)	2.44 ± 0.93	2.42 ± 0.91
Total cholesterol (mmol/l)	4.50 ± 1.10	4.49 ± 1.09
Triglycerides (mmol/l)	2.08 ± 1.58	2.19 ± 1.91
Vascular disorders	577 (74.6)	186 (42.4)
Hypertension	561 (72.6)	182 (70.8)
Arteriosclerosis	9 (1.2)	3 (1.2)
Antidiabetic treatment at screening		
Metformin monotherapy	212 (27.4)	88 (34.2)
Metformin ± (sulfonylurea or glinides) ± α-glucosidase inhibitor	428 (55.4)	122 (47.5)
Metformin ± DPP-4 inhibitor ± (sulfonylurea or glinides) ± α-glucosidase inhibitor	133 (17.2)	47 (18.3)

Data are n, n (%), or mean ± SD. Data are for the full analysis set except for lipids and blood pressure, which are for the safety analysis set.

Mean weight gain was similar (3.6 vs. 4.0 kg, respectively).

Study Limitations

Each trial was conducted as an open-label study because blinded insulin pen devices are not available. This introduced potential bias into subjective outcomes such as patient-reported hypoglycemia and, for Study A, SF-36 surveys. It is notable that previous treat-to-target trials were open-label and still widely accepted.[3,4]

Potential bias was also introduced at the initiation of Study B. In patients previously taking basal insulin more than once a day, the dose was reduced 20–30% before switching to once-daily glargine. However, for patients randomized to degludec, dosage reductions were at the investigator's discretion, and a reduction was not required.

Additional insulin dosing variability resulted from investigator discretion in the treat-to-target design. Although a prespecified FPG titration schedule was provided, < 50% of subjects in either trial achieved the goal FPG of 70–90 mg/dl. This indicates that this level of control may have been tighter

Table 4. Study B: Select Baseline Characteristics	Insulin Degludec	Insulin Glargine
Participants randomly assigned treatment (full analysis set)	744	248
Participants exposed to treatment (safety analysis set)	753	251
Male	405 (54)	133 (54)
Race		
White	619 (83)	203 (82)
Black	67 (9)	27 (11)
Asian	50 (7)	13 (5)
Other	8 (1)	5 (2)
Ethnicity: Hispanic or Latin American	87 (12)	32 (13)
Age (years)	59.2 ± 9.1	58.1 ± 10.0
Body weight (kg)	92.6 ± 17.9	92.2 ± 17.2
BMI (kg/m^2)	32.3 ± 4.7	31.9 ± 4.5
Duration of diabetes (years)	13.6 ± 7.4	13.4 ± 6.9
A1C (%)	8.3 ± 0.8	8.4 ± 0.9
Systolic blood pressure (mmHg)	132.8 ± 15.2	132.8 ± 14.0
Diastolic blood pressure (mmHg)	76.7 ± 9.5	77.4 ± 8.0
HDL cholesterol (mmol/l)	1.2 ± 0.3	1.3 ± 0.4
LDL cholesterol (mmol/l)	2.5 ± 0.9	2.5 ± 0.9
Triglycerides (mmol/l)	2.0 ± 1.4	1.8 ± 1.2
Insulin regimen		
Basal-bolus insulin ± OAD	362 (49)	124 (50)
Basal-bolus insulin (< 2 per day) ± OAD	19 (3)	3 (1)
Premix therapy ± OAD	181 (24)	61 (25)
Basal insulin ± OAD	154 (21)	56 (23)
Bolus insulin ± OAD	28 (4)	4 (2)
OAD regimen		
1	340 (46)	130 (52)
2	124 (17)	28 (11)
> 2	15 (2)	7 (3)

Data are n, n (%), or mean ± SD. Data are for the full analysis set except for lipids and blood pressure, which are for the safety analysis set. OAD, oral antidiabetic drug.

than what some providers consider a comfortable target. The definite impact of this cannot be assessed because individual subjects' dosing regimens are not available. However, should current practitioners seek to meet the prespecified FPG goal, it is possible that rates of hypoglycemia may vary from those documented in the trials.

Practice Implications
Degludec is undergoing further review by the FDA to address concerns raised about its cardiovascular safety in an FDA meta-analysis of 16

phase 3 trials.[5] In Study A, 89 cardiac events were reported. Event rates were 0.1 and 0.09 events/PYE for degludec and glargine, respectively. Table 3 shows select baseline characteristics, including cardiovascular risk factors.

Results were similar for Study B, with event rates of 3 and 2 events/100 PYE for the degludec and glargine groups, respectively. Table 4 shows select baseline characteristics, including cardiovascular risk factors.

The only potential treatment-related death was a myocardial infarction reported in the glargine group in Study B. In Study A, one event of sudden cardiac death was reported in the degludec group, but this occurred 11 days after stopping treatment and was considered unrelated to treatment. Although these trials did not show a significant increase in cardiovascular events with degludec use, the meta-analysis revealed a major adverse cardio-vascular event (MACE) incidence rate of 1.48 with degludec compared to 1.44 with comparator. MACEs included cardiovascular death, stroke, and acute coronary syndrome (myocardial infarction and unstable angina pectoris). Additional research is underway, and results will affect degludec approval in the United States. Of note, degludec is already approved in Europe and Japan.

If approved in the Untied States, insulin degludec will offer a novel option for insulin therapy. Other trials have shown it to have an extended duration of action (exceeding 42 hours)[6] and flexibility of dosing time, without evidence of accumulation (commonly known as "stacking").[7] These characteristics may improve glycemic control in patients who miss doses or have variable schedules that make dosing at the same time each day difficult. Perhaps of greatest significance are that its low rates of overall and nocturnal hypoglycemia may help to address an important barrier to insulin therapy among both patients and health care providers. The decrease in hypoglycemia risk with degludec continues the trend observed with succeeding generations of basal insulin.

In summary, degludec appears to offer important benefits over basal insulin analogs that may make it an important treatment option for patients with type 2 diabetes.

REFERENCES
[1]Turner RC, Cull CA, Frighi V, Holman RR: Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). *JAMA* 281:2005–2012, 1999

[2]Wild D, von Maltzahn, Brohan E, Christensen T, Clauson P, Gonder-Frederick L: A critical review of the literature on fear of hypoglycemia in diabetes: implications for diabetes management and patient education. *Patient Educ Couns* 68:10–15, 2007

[3]Riddle MC, Rosenstock J, Gerich J: The Treat-to-Target Trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 26:3080–3086, 2003

[4]Hermansen K, Davies M, Derezinski T, Martinez Ravn G, Clauson P, Home P, on behalf of the Levemir Treat-to-Target Study Group: A 26-week, randomized, paral-lel, treat-to-target trial comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetes Care* 29:1269–1274, 2006

[5]U.S. Food and Drug Administra-tion: FDA briefing document: NDA 203313 and NDA 203314 insulin degludec and insulin degludec/aspart, 8 Novem-ber 2012. Available from http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM327015.pdf. Accessed 2 August 2013

[6]Jonassen I, Havelund S, Hoeg-Jensen T, Steensgaard DB, Wahlund P: Design of the novel protraction mechanism of insulin degludec, an ultra-long-acting basal insulin. *Pharm Res* 229:2104–2114, 2012

[7]Mathieu C, Hollander P, Miranda-Palma B, Cooper J, Franek E, Russell-Jones D, Larsen J, Can Tamer S, Bain SC, on behalf of the NN1250-3370 (BEGIN: Flex T1) Trial Investigators: Efficacy and safety of insulin degludec in a flexible dosing regimen vs insu-lin glargine in patients with type 1 diabetes (BEGIN: Flex 1): a 26-week randomized, treat-to-target trial with a 26-week extension. *J Clin Endocrinol Metab* 98:1154–1162, 2013

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