

## Combination Oral/Insulin Therapy

### 5 Initiating Insulin Therapy with Insulin Detemir in Insulin-Naïve, Oral Antidiabetic Agent-Treated Patients with Type 2 Diabetes Mellitus Improves Glycemic Control without Weight Gain: Data from a German Subgroup of the PREDICTIVE Study

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**Background:** Insulin initiation may induce weight gain, as well as increase insulin resistance and risk for cardiovascular events, in patients with type 2 diabetes mellitus (DM).

**Objective:** To evaluate the safety and efficacy of insulin detemir, a basal-insulin analogue, in clinical practice.

**Methods:** This report presents baseline and 3-month follow-up data from 1321 insulin-naïve patients with type 2 DM started on insulin detemir (± oral antidiabetic drugs [OADs]) in the large, multicenter, prospective, observational Predictable Results and Experience in Diabetes through Intensification and Control to Target: An International Variability Evaluation (PREDICTIVE) study.

Patient demographic characteristics at baseline were: male, 50.6%; mean age, 62.2 years; duration of DM, 6.5 years; glycosylated hemoglobin (A1C) level, 8.49%; body mass index, 29.5 kg/m<sup>2</sup>. The percentage of patients using OADs at baseline was: metformin (72%), sulfonylureas (37%), glinides (24%), alpha-glucosidase inhibitors (8%), and thiazolidinediones (5%).

**Results:** At follow-up, reductions from baseline in A1C level (8.49% to 7.20%), fasting blood glucose (FBG) (183 to 125 mg/dL), and within-subject variability in FBG (SD of FBG) (20.4 to 12.2 mg/dL) were observed. Mean body weight decreased (86.1 to 85.2 kg). Rate of hypoglycemic events at follow-up was lower than at baseline (0.3 vs 1.4 events per patient/year). The majority (82%) of patients were taking once-daily insulin detemir; 84% used insulin detemir with OADs. The percentage of patients using OADs at follow-up was similar compared with baseline: metformin (75%), sulfonylureas (43%), glinides (13%), alpha-glucosidase inhibitors (6%), and thiazolidinediones (3%).

**Conclusion:** In insulin-naïve patients with type 2 DM, initiating insulin therapy with insulin detemir improved glycemic control without weight gain or increased rates of hypoglycemia.

### 6 Basal-Bolus Therapy Using Insulin Glargine and Insulin Glulisine Improves Metabolic Control in Everyday Clinical Practice in Patients with Type 1 Diabetes Mellitus

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**Objective:** To examine the effects of insulin glulisine plus insulin glargine as basal-bolus therapy in everyday clinical practice in patients with inadequately controlled type 1 and type 2 diabetes mellitus (DM).

**Methods:** This 12-week, uncontrolled, observational study, with follow-up after 6 months, presents data for 1447 patients with type 1 DM whose blood glucose (BG) level was poorly controlled with their previous insulin regimen. Patients received 1 to 3 daily injections of insulin glulisine in combination with once-daily insulin glargine. Insulin-dosing decisions were made at the physicians' discretion.

**Results:** Mean ± SD demographic characteristics were: age, 42.6 ± 14.5 years; duration of DM, 16.8 ± 12.8 years; 91.3% of patients were receiving 3 injections of insulin glulisine daily. Glycemic parameters had already improved from baseline by week 12 and remained low at 6 months (Table). All data are mean ± SD. A total of 16 patients reported adverse events; 13 patients reported hypoglycemia (0.9% of the study population).

**Table.**

	A1C, %	Fasting Blood Glucose, mg/dL (mM)	2-Hour Postprandial Blood Glucose at Breakfast, mg/dL (mM)	Total Daily Glulisine Dose, U	Total Daily Glargine Dose, U
Baseline	8.0 ± 1.4 (n = 1435)	153.2 ± 45.1 (8.5 ± 2.5)	175.8 ± 47.3 (9.8 ± 2.6)	–	–
12 Weeks	7.1 ± 0.9* (n = 1342)	117.3 ± 29.6 (6.5 ± 1.6)	134.1 ± 30.7 (7.5 ± 1.7)	29.5 ± 13.6	22.6 ± 10.0
6 Months	6.9 ± 0.9 (n = 805)	115.8 ± 28.0 (6.4 ± 1.6)	134.6 ± 31.0 (7.5 ± 1.7)	29.8 ± 13.0	22.8 ± 9.7

A1C = glycosylated hemoglobin.

\*Baseline–endpoint: –1.0% ± 1.2% (n = 1360), P < 0.0001

**Conclusion:** These results from everyday practice are consistent with experience obtained in clinical trials. The overall data suggest that insulin glulisine, combined with insulin glargine, may contribute to good and stable BG control with low rates of hypoglycemic events in patients with type 1 DM.

## 7 Basal-Bolus Therapy Using Insulin Glargine and Insulin Glulisine Improves Metabolic Control in Everyday Clinical Practice in Patients with Type 2 Diabetes Mellitus

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**Objective:** To examine the effects of insulin glulisine combined with insulin glargine as basal-bolus therapy in patients with inadequately controlled type 2 diabetes mellitus (DM).

**Methods:** This 12-week, uncontrolled, observational study, with follow-up after 6 months, presents data for 5695 patients with type 2 DM whose blood glucose (BG) level was poorly controlled with their previous insulin regimen with or without oral antidiabetic drugs (OADs). Patients received 1 to 3 daily injections of insulin glulisine in combination with once-daily insulin glargine. Dosing decisions and continuation of OADs were made at the physicians' discretion.

**Results:** Mean  $\pm$  SD demographic characteristics were: age,  $61.8 \pm 10.5$  years; duration of DM,  $10.6 \pm 7.4$  years; 92.5% of patients were receiving 3 injections of glulisine daily. Glycemic parameters had already improved from baseline by week 12 and remained stable at 6 months (Table). All data are mean  $\pm$  SD. A total of 82 patients reported adverse events; 38 patients reported hypoglycemia (0.7% of the study population).

Table.

	A1C, %	Fasting Blood Glucose, mg/dL (mM)	2-Hour Postprandial Blood Glucose at Breakfast, mg/dL (mM)	Total Daily Glulisine Dose, U	Total Daily Glargine Dose, U
Baseline	8.3 $\pm$ 1.3 (n = 5645)	171.6 $\pm$ 41.9 (9.5 $\pm$ 2.3)	196.4 $\pm$ 44.6 (10.9 $\pm$ 2.5)	–	–
12 Weeks	7.3 $\pm$ 0.9* (n = 5284)	124.4 $\pm$ 27.6 (6.9 $\pm$ 1.5)	139.3 $\pm$ 29.5 (7.7 $\pm$ 1.6)	39.2 $\pm$ 24.8	26.5 $\pm$ 14.1
6 Months	7.0 $\pm$ 0.9 (n = 3161)	122.4 $\pm$ 26.0 (6.8 $\pm$ 1.4)	138.0 $\pm$ 30.2 (7.7 $\pm$ 1.7)	39.3 $\pm$ 24.1	26.2 $\pm$ 14.1

A1C = glycosylated hemoglobin.

\*Baseline–endpoint:  $-1.2\% \pm 1.0\%$  (n = 5340),  $P < 0.0001$ .

**Conclusion:** These results from everyday practice are consistent with experience obtained in clinical trials. The overall data suggest that insulin glulisine, combined with insulin glargine, may contribute to good and stable BG control with low rates of hypoglycemic events in patients with type 2 DM.

## 8 The Combination of Prandial Insulin Glulisine and Once-Daily Insulin Glargine Effectively Lowers Glycemic Parameters in Patients with Type 1 Diabetes Mellitus

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**Objective:** To examine the efficacy and safety of daily prandial glulisine plus once-daily insulin glargine in patients with type 1 diabetes mellitus (DM) who previously received other short-, medium-, or long-acting insulin or combined insulin therapy.

**Methods:** A 26-week, multicenter, open-label study was performed in 60 patients with type 1 DM (glycosylated hemoglobin [A1C] level, 6.5%–11%; body mass index,  $<35$  kg/m<sup>2</sup>; age,  $34.7 \pm 1.4$  years; duration of DM,  $12.7 \pm 1.2$  years). All baseline characteristics are mean  $\pm$  SD. Patients were administered once-daily insulin glargine plus their previous prandial insulin for 4 weeks before the treatment phase to establish baseline values. During the 26-week treatment period, insulin glulisine was administered 3 to 6 times daily in place of the previous prandial insulin. A1C levels and daily fasting, premeal, and postmeal blood glucose (BG) glycemic profiles were measured.

**Results:** A1C values decreased significantly from  $9.1 \pm 0.2\%$  at baseline to  $7.6 \pm 0.2\%$  at endpoint ( $P < 0.0001$ ). Fasting and postprandial BG values decreased from baseline (Table). Mean insulin glargine and glulisine doses remained unchanged (mean [U/day] baseline/endpoint: 19.3/20.9 and 24.2/25.1, respectively). The number of patients with nocturnal hypoglycemia (1.4 to 3.9 mM) decreased from 18.1% at baseline to 8.8% at endpoint. Both insulins were well tolerated.

**Conclusion:** Once-daily insulin glargine plus prandial glulisine significantly reduced A1C values, postprandial BG level, and nocturnal hypoglycemia, suggesting that this regimen may help improve glycemic control in patients with type 1 DM.

Table.

Blood Glucose (time measured)	Mean Baseline/Endpoint, mM
Fasting	8.6/6.9*
After breakfast	9.0/8.3†
Before lunch	8.3/7.7
After lunch	9.4/8.2†
Before dinner	8.3/7.8†
After dinner	9.4/8.6†
Bedtime	9.3/8.5†
3:00 AM	9.2/7.4

\* $P < 0.001$  mean baseline–end point change.

† $P < 0.05$ .

## 9 Basal Insulin and Oral Antidiabetic Therapy (BOT) Plus a Single Dose of Insulin Glulisine (BOT+) Reduces Glycosylated Hemoglobin Levels and Preprandial and Postprandial Blood Glucose Values in Patients with Type 2 Diabetes Mellitus

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**Objective:** To examine the efficacy of once-daily insulin glargine as basal insulin in basal insulin and oral antidiabetic drug (OAD) therapy (BOT), plus a single daily prandial dose of insulin glulisine (BOT+) in patients with type 2 diabetes mellitus (DM).

**Methods:** A 26-week ongoing study was performed in 158 patients with type 2 DM who were undergoing BOT (insulin glargine titration to fasting blood glucose [FBG] >120 mg/dL) yet demonstrating unsatisfactory glycosylated hemoglobin [A1C] levels (>6.5% ± 9.0%). Patients were randomized to the BOT+ regimen with insulin glulisine administered at breakfast or the BOT+ regimen with insulin glulisine taken at the predominant meal. OADs remained unchanged during the study.

**Results:** Blinded data monitoring revealed an overall reduction in mean A1C level (baseline/endpoint: 7.4/7.0%), with 26.0% of patients achieving A1C levels of <6.5% at endpoint. Eight-point preprandial and postprandial blood glucose (BG) values, except FBG, decreased (Table). Mean insulin glargine dose remained unchanged (mean [U/day] baseline/endpoint: 30/31); whereas insulin glulisine dose increased (5/11). There were 163 confirmed hypoglycemic events (BG <60 mg/mL) during treatment, representing 2.52 hypoglycemic events per patient/year.

**Conclusion:** The BOT+ regimen decreased both A1C and postprandial BG levels, suggesting that this regimen may help improve glycemic control in patients with type 2 DM. The final comparison of prandial glulisine efficacy at breakfast versus the predominant meal, along with hypoglycemic events and other safety data, awaits study completion.

**Table.**

Blood Glucose (time measured)	Mean Baseline/Endpoint, mg/dL
Fasting	111/118*
After breakfast	177/148*
Before lunch	131/119*
After lunch	171/154*
Before dinner	149/141*
After dinner	185/165*
Bedtime	166/148*
3:00 AM	122/118

\* $P < 0.05$  mean baseline–endpoint change.

## 10 Once-Daily Insulin Detemir Improves Glycemic Control as Much as Neutral Protamine Hagedorn Insulin When Added to Oral Antidiabetic Drugs in Patients with Type 2 Diabetes Mellitus, but with Reduced Hypoglycemia and Less Weight Gain

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**Background:** Insulin therapy is often initiated in patients with poorly controlled type 2 diabetes mellitus (DM) by adding a basal formulation to oral antidiabetic drug (OAD) therapy. Used this way, and given twice daily, insulin detemir is as effective as neutral protamine Hagedorn (NPH) insulin in improving glycemic control but with reduced hypoglycemia and less weight gain. Pharmacologic data suggest that insulin detemir should also be effective when given once daily.

**Objective:** To assess the effectiveness of once-daily morning or evening dosing with insulin detemir in patients with poorly controlled type 2 DM taking OADs.

**Methods:** This multicenter, 20-week, 3-arm, parallel-group, noninferiority trial randomly assigned 504 insulin-naïve patients to receive an evening injection of insulin detemir, a prebreakfast injection of insulin detemir, or an evening injection of NPH (1:1:1).

**Results:** An evening or morning injection of insulin detemir produced similar reductions in glycosylated hemoglobin (A1C) level compared with an evening dose of NPH (raw mean decreases: -1.6%, -1.5%, and -1.7%, respectively). Compared with NPH, an evening injection of insulin detemir reduced confirmed all-day and nocturnal hypoglycemia by 53% ( $P = 0.019$ ) and 65% ( $P = 0.031$ ), respectively. Incidence of hypoglycemia did not differ statistically between patients receiving morning and evening doses of insulin detemir, but nocturnal hypoglycemia was reduced by 87% in patients receiving a morning dose of insulin detemir compared with those receiving an evening dose of NPH ( $P < 0.001$ ). Weight gain was 1.1, 0.7, and 1.6 kg with a morning dose of insulin detemir, an evening dose of insulin detemir, and NPH, respectively (evening dose of insulin detemir vs NPH:  $P = 0.005$ ). All regimens were well tolerated, with no major adverse events reported.

**Conclusion:** An evening injection of insulin detemir, added to an OAD regimen, results in reduced hypoglycemia and less weight gain compared with NPH. A morning injection of insulin detemir achieves similar overall glycemic control with a very low incidence of nocturnal hypoglycemia, but it results in higher weight gain than does NPH or an evening injection of insulin detemir.