Pramlintide Improved Glycemic Control and Reduced Weight in Patients With Type 2 Diabetes Using Basal Insulin

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OBJECTIVE — To assess the efficacy and safety of pramlintide in patients with type 2 diabetes suboptimally controlled with basal insulin.

RESEARCH DESIGN AND METHODS — In a 16-week, double-blind, placebo-controlled study, 212 patients using insulin glargine with or without oral antidiabetes agents (OAs) were randomized to addition of pramlintide (60 or 120 μg b.i.d./t.i.d.) or placebo. Insulin glargine was adjusted to target a fasting plasma glucose concentration of 70–100 mg/dl. One coprimary end point was the change in A1C at week 16. The other coprimary end point was a composite measure of overall diabetes control comprising A1C ≤7.0% or reduction ≥0.5%, mean daily postprandial glucose (PPG) increments ≤40 mg/dl, no increase in body weight, and no severe hypoglycemia. Patients meeting all four conditions at week 16 achieved this end point.

RESULTS — More pramlintide- than placebo-treated patients achieved the composite end point (25 vs. 7%; $P < 0.001$). Reductions (means ± SE) in A1C (−0.70 ± 0.11% vs. −0.36 ± 0.08%; $P < 0.05$) and PPG increments (−24.4 ± 3.6 mg/dl vs. −0.4 ± 3.0 mg/dl; $P < 0.0001$) were greater in pramlintide- versus placebo-treated patients, respectively. Glycemic improvements were accompanied by progressive weight loss with pramlintide and weight gain with placebo (−1.6 ± 0.3 kg vs. +0.7 ± 0.3 kg; $P < 0.0001$). No treatment-related severe hypoglycemia occurred.

CONCLUSIONS — Pramlintide improved multiple glycemic parameters and reduced weight with no increase in hypoglycemia in patients with type 2 diabetes who were not achieving glycemic targets with basal insulin with or without OAs.

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Type 2 diabetes is characterized by insulin resistance and progressive β-cell dysfunction resulting in deficiencies of insulin and amylin. Due to the progressive nature of the disease, therapy for most patients starts with medical nutrition therapy and exercise and is followed by the addition of one or more oral antidiabetes agents (OAs). Insulin, usually a basal, long-acting preparation, is eventually required to achieve adequate glycemic control. While basal insulin therapy can result in adequate fasting glucose control, it does not address postprandial hyperglycemia (1,2). Even with rigorous basal insulin titration, ~30–40% of patients do not reach acceptable A1C levels (≤7.0%) (3,4). For those not achieving glycemic targets, intensification of therapy with the addition of mealtime insulin increases the risk of hypoglycemia (5–7) and often results in undesirable weight gain (8–10).

Pramlintide is a synthetic analog of human amylin, a naturally occurring neuroendocrine hormone cosecreted with insulin by pancreatic β-cells (11). Amylin regulates gastric emptying (12), suppresses inappropriate postprandial glucagon secretion (13), and reduces food intake (14,15). Through mechanisms similar to those of amylin, pramlintide reduces postprandial glucose (PPG), improving overall glycemic control (16,17), and increases satiety, resulting in reduced food intake and weight loss (16–19).

Therapies that improve glycemic control without weight gain and its associated long-term complications and do not increase the risk of severe hypoglycemia will significantly enhance treatment of patients with type 2 diabetes. This study investigated the efficacy and safety of pramlintide therapy with basal insulin titration in patients with type 2 diabetes suboptimally controlled with basal insulin, with or without OAs.

RESEARCH DESIGN AND METHODS

— Enrolled patients were aged 25–75 years with type 2 diabetes and not achieving adequate glycemic control with insulin glargine (no mealtime insulin), with or without OA therapy (metformin, sulfonylurea, and/or thiazolidinedione). Inclusion criteria at screening included A1C >7.0% and ≤10.5%, BMI 25–45 kg/m^2, insulin glargine treatment ≥3 months with a stable dose (±10%) for ≥1 month, and, if applicable, a stable dose of OAs for ≥2 months. Female patients were postmenopausal, surgically sterile, or used adequate contraception throughout the study. Patients were excluded if they had a history of hypoglycemia unawareness or recurrent severe hypoglycemia during the preceding 6 months, were participating in a weight loss program, were using antiobesity agents, or had a confirmed diagnosis of gastroparesis or any other significant medical condition.

The study protocol was approved by

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Abbreviations: FPG, fasting plasma glucose; OA, oral antidiabetes agent; PPG, postprandial glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

an institutional review board. All patients provided written informed consent before study initiation. The study was conducted in accordance with principles outlined in the Declaration of Helsinki (1964), including all amendments through the South Africa revision (1996).

This was a 16-week, randomized, double-blind, placebo-controlled, multicenter study conducted in the U.S. (41 sites) between October 2005 and June 2006. After a screening visit, eligible patients made six visits to the study site (baseline, 2, 4, 8, 12, and 16 weeks). At the baseline visit, patients were randomized to receive pramlintide (Amylin Pharmaceuticals, San Diego, CA) or placebo (Amylin Pharmaceuticals). Randomization was stratified according to screening visit A1C (≤8 or >8%), BMI (≤35 or >35 kg/m^2), and sulfonylurea use (yes/no).

Study medication (pramlintide or placebo) was self-administered subcutaneously immediately before major meals depending on the patient's typical meal pattern (b.i.d. or t.i.d.). Patients initiated study medication at a volume equivalent to 60 μg pramlintide per dose and escalated to a volume equivalent to 120 μg per dose within 3–7 days if no clinically significant nausea occurred. Once the maintenance dose was achieved, investigators were asked to make weekly adjustments in the insulin glargine dose to target a fasting glucose concentration of ≥70 to <100 mg/dl using an algorithm previously described by Riddle et al. (3). Patients self-monitored fasting glucose concentrations daily and completed two self-monitored, seven-point glucose profiles during the week before each visit consisting of measurements taken 15 min before and 1.5–2 h after the start of each meal and at bedtime. Patients were required to eat three meals on profile days. Patients used study-provided Accu-Chek Aviva blood glucose monitors (Roche Diagnostics, Indianapolis, IN), reporting plasma-referenced glucose concentrations. At each visit, weight and vital signs were measured and self-monitored blood glucose values, insulin dose, and adverse events reviewed. A1C was measured at screening, baseline, and every 4 weeks thereafter. Laboratory measurement of fasting plasma glucose (FPG) was performed at baseline and week 16. Patients were instructed to maintain their usual diet and exercise regimens throughout the study.

Study end points

Two coprimary end points were evaluated in this study. The first coprimary end point was the change in A1C from baseline to week 16. The second coprimary end point was a dichotomous composite end point assessing the proportion of patients meeting all of the following prespecified criteria at week 16: *1*) A1C ≤7.0% or an A1C reduction from baseline ≥0.5%, *2*) mean daily PPG increments ≤40 mg/dl, *3*) no weight gain, and *4*) no severe hypoglycemia. Severe hypoglycemia was defined as a hypoglycemic event requiring assistance from another individual and/or administration of glucagon or intravenous glucose. Secondary end points included components of the composite end point, the proportion of patients achieving A1C ≤7.0 or ≤6.5% and changes from baseline to each time point in A1C, seven-point glucose profiles, PPG increments, FPG, weight, and insulin glargine dose. Similar ad hoc analyses for secondary end points were performed on patients divided into subgroups according to baseline A1C ≤8.5 or >8.5%.

Statistical analyses

A sample size of 90 patients per treatment arm was predicted to provide ~90% power to detect a difference in the proportion of patients achieving the coprimary composite end point and ~95% power to demonstrate noninferiority of pramlintide versus placebo for change in A1C from baseline. Noninferiority for change in A1C was concluded if the upper limit of the two-sided 95% CI for the difference between pramlintide and placebo was below the noninferiority margin of 0.4%. The overall power for reaching both coprimary end points was expected to be ~85%. As both coprimary end points were required to be met, no adjustment to the significance level ($\alpha = 0.05$) was required.

Analyses were performed on patients within the intent-to-treat population, all of whom received at least one dose of study medication. Missing individual data were imputed from the last scheduled visit using the last-observation-carried-forward approach for all efficacy analyses, with the exception of FPG, insulin dose, and the seven-point glucose profiles that were analyzed using the intent-to-treat observed population. Fisher's exact test was used to compare the proportion of patients achieving the coprimary composite and secondary binary end points. A general linear model including treatment, baseline A1C stratum (≤8.0 or >8.0%), BMI stratum (≤35 or >35 kg/m^2), and sulfonylurea use (yes/no) as covariates was used to compare the change in A1C at week 16. Parametric analyses of secondary continuous end points were performed using general linear models including treatment and baseline value as covariates. Descriptive analyses and *P* values used the arithmetic and least squares means, respectively.

RESULTS

Patient disposition and baseline demographics

Of 212 patients randomized, 91 (85%) placebo-treated and 87 (83%) pramlintide-treated patients completed the study (Table 1). One patient in the placebo-treated arm withdrew consent before injection of study medication, resulting in an intent-to-treat population of 211 patients. Baseline demographics were well matched between treatment arms (Table 1). Eighty-nine percent used at least one OA, and 50% used two or three OAs. Within the pramlintide-treated population, 98 (93%) patients escalated to the 120-μg dose.

Coprimary end points

A1C. A1C values progressively decreased throughout the study. Pramlintide-treated patients achieved a significantly ($P < 0.05$) greater reduction (means ± SE) from baseline at week 16 (−0.70 ± 0.11%) than placebo-treated patients (−0.36 ± 0.08%), exceeding the noninferiority criterion (upper limit of 95% CI = −0.04%) (Fig. 1*A*). Mean (±SE) A1C values at week 16 were 7.8 ± 0.1% (pramlintide) and 8.1 ± 0.1% (placebo). The proportion of patients achieving an A1C ≤7.0 or ≤6.5% was 23 and 11% with pramlintide and 13 and 4% with placebo, respectively.

Composite end point. At week 16, significantly more pramlintide-treated patients achieved the composite end point than placebo-treated patients (25 vs. 7%; $P < 0.001$) (Fig. 1*B*).

Secondary end points

Components of the composite end point. The percentage of pramlintide- versus placebo-treated patients achieving an A1C ≤7.0% or an A1C reduction ≥0.5% was not significantly different (Fig. 1*C*). Significantly more pramlintide-treated patients achieved mean PPG increments ≤40 mg/dl ($P < 0.0001$) and

Table 1—*Patient disposition and baseline demographics*

	Total population		Placebo baseline A1C		Pramlintide baseline A1C	
	Placebo	Pramlintide	≤8.5%	>8.5%	≤8.5%	>8.5%
Disposition (*n*)						
Randomized	107	105	59	48	63	42
Completed	91	87	51	40	52	35
Withdrew	16	18	8	8	11	7
Reason for withdrawal						
Withdrawal of consent	12	9	5	7	6	3
Adverse event	1	4	1	0	3	1
Investigator decision	3	0	2	1	0	0
Protocol violation	0	2	0	0	1	1
Lost to follow-up	0	3	0	0	1	2
Baseline demographics						
Intent-to-treat population (*n*)	106	105	58	48	63	42
Sex (male/female) (*n*)	55/51	48/57	35/23	20/28	32/31	16/26
Race (Caucasian/other) (*n*)	77/29	77/28	40/18	37/11	47/16	30/12
Age (years)	55 ± 10	55 ± 9	55 ± 11	56 ± 9	56 ± 8	53 ± 9
Weight (kg)	103 ± 18	103 ± 18	105 ± 20	99 ± 16	104 ± 18	102 ± 16
BMI (kg/m^2)	35 ± 6	35 ± 5	35 ± 6	35 ± 6	35 ± 5	36 ± 4
Diabetes duration (years)	10 ± 6	11 ± 6	10 ± 6	11 ± 6	11 ± 6	11 ± 6
A1C (%)	8.5 ± 0.9	8.5 ± 0.9	7.7 ± 0.4	9.3 ± 0.6	7.9 ± 0.4	9.4 ± 0.7
FPG (mg/dl)	140 ± 54	146 ± 52	133 ± 57	150 ± 50	132 ± 45	167 ± 56
PPG increments (mg/dl)	57 ± 27	59 ± 29	58 ± 29	56 ± 26	58 ± 28	62 ± 32
OA use (*n*)	96	92	54	42	59	33
Sulfonylurea use (no/yes) (*n*)	50/56	54/51	26/32	24/24	30/33	24/18
Daily insulin dose (units)	54 ± 42	48 ± 25	57 ± 43	51 ± 42	44 ± 22	55 ± 29

Data are means ± SD, unless otherwise indicated.

did not gain weight ($P < 0.0001$). Compared with placebo, more pramlintide-treated patients achieved both A1C and PPG components ($P < 0.005$), more reached the A1C goal without weight gain ($P < 0.0001$), and more had well-controlled PPG without weight gain ($P < 0.0001$) (Fig. 1*D*). One episode of severe hypoglycemia occurred in a pramlintide-treated patient but was deemed unrelated to pramlintide treatment by the investigator.

Insulin. Insulin glargine dosage increased steadily throughout the study (Fig. 2*A*). Mean (±SE) week 16 dosage was 61.4 ± 3.4 units (pramlintide) and 69.5 ± 5.3 units (placebo), reflecting increases of 11.7 ± 1.9 units and 13.1 ± 1.6 units, respectively.

Fasting plasma glucose. Mean (±SE) FPG concentrations at week 16 were 119.5 ± 4.1 mg/dl (pramlintide) and 122.8 ± 4.3 mg/dl (placebo), reflecting an average change from baseline of −28.3 ± 6.8 mg/dl (pramlintide) and −12.0 ± 5.6 mg/dl (placebo). An FPG concentration <100 mg/dl was achieved by 28 of 105 (27%) pramlintide-treated and 33 of 106 (31%) placebo-treated patients at week 16.

PPG increments. Mean (±SE) PPG increments at week 16 were 34.8 ± 2.7 mg/dl (pramlintide) and 56.6 ± 2.3 mg/dl (placebo), reflecting significant decreases in PPG increments from baseline to week 16 in pramlintide- versus placebo-treated patients (−24.4 ± 3.6 mg/dl [pramlintide] vs. −0.4 ± 3.0 mg/dl [placebo]) ($P < 0.0001$) (Fig. 2*B*).

Weight. Pramlintide treatment resulted in progressive weight loss, while placebo-treated patients gained weight (week 16: −1.6 ± 0.3 kg vs. 0.7 ± 0.3 kg, $P < 0.0001$) (Fig. 2*C*). At week 16, approximately two-thirds (68%) of pramlintide-treated patients had lost weight compared with approximately one-third (35%) of placebo-treated patients ($P < 0.0001$) (Fig. 2*D* and *E*).

Patient stratification according to baseline A1C

To further explore the implications of these results in clinical practice, we divided the study population into two subgroups according to the mean baseline A1C (≤8.5 or >8.5%) (Table 1). These subgroups were similar in baseline characteristics, except for mean A1C (7.8 vs. 9.4%) and mean FPG (132 vs. 158 mg/dl). Insulin glargine dosage increased steadily from baseline to week 16 in both subgroups.

Baseline A1C ≤8.5%. At week 16, pramlintide-treated patients exhibited reductions from baseline in mean (±SE) A1C (−0.36 ± 0.13%), FPG (−17.3 ± 7.1 mg/dl), PPG increments (−24.9 ± 4.4 mg/dl), and weight (−2.0 ± 0.4 kg). In contrast, placebo-treated patients exhibited a reduction from baseline in mean (±SE) FPG (−7.5 ± 6.8 mg/dl) but did not exhibit changes from baseline in A1C (−0.08 ± 0.09%), PPG increments (−3.6 ± 3.8 mg/dl), or weight (0.4 ± 0.4 kg).

Baseline A1C >8.5%. At week 16, pramlintide-treated patients exhibited reductions from baseline in mean (±SE) A1C (−1.19 ± 0.14%), FPG (−44.4 ± 12.7 mg/dl), PPG increments (−23.7 ± 5.9 mg/dl), and weight (−1.0 ± 0.3 kg). Placebo-treated patients exhibited reductions from baseline in mean (±SE) FPG (−18.4 ± 9.4 mg/dl) and A1C (−0.69 ± 0.13%) but did not exhibit a change in PPG increments (3.2 ± 4.6 mg/dl), and they gained weight (1.1 ± 0.4 kg). The

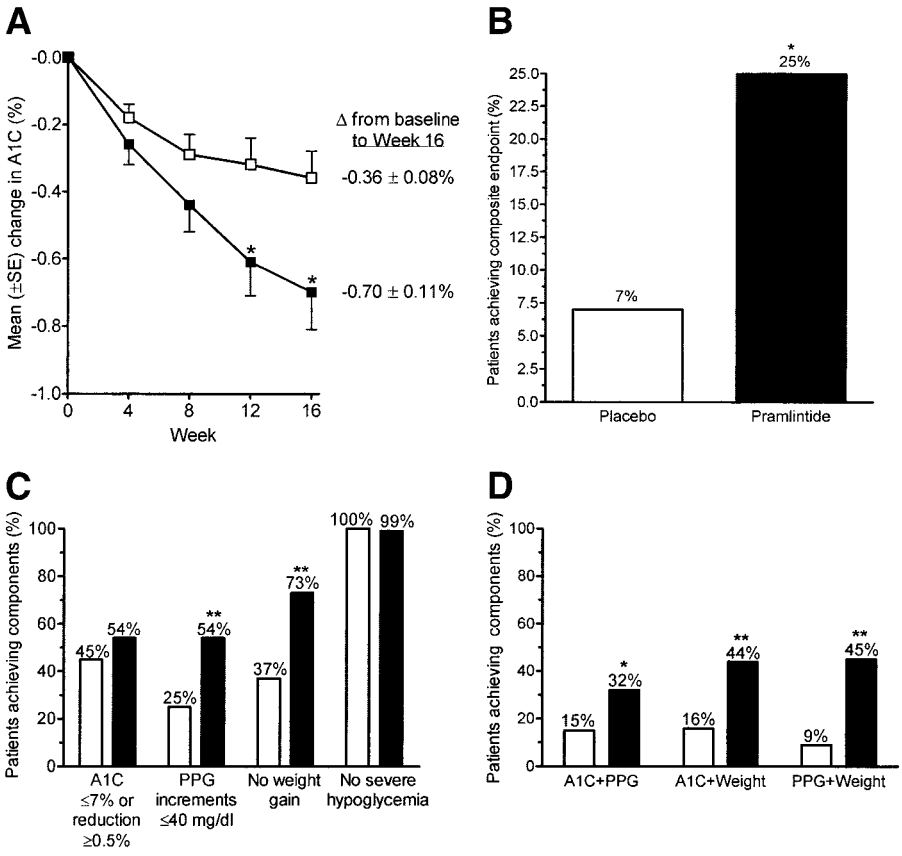

Figure 1—A: *Mean (±SE) change in A1C from baseline to each visit.* *P < *0.05 for pramlintide vs. placebo.* □, *placebo;* ■, *pramlintide.* B: *Percentage of patients achieving the composite end point at week 16.* C: *Percentage of patients achieving each component within the composite end point at week 16.* □, *placebo;* ■, *pramlintide.* D: *Percentage of patients achieving at least two components, not including severe hypoglycemia, within the composite end point at week 16.* □, *placebo;* ■, *pramlintide.* B–D: *P < 0.005; **P < 0.0001 for pramlintide vs. placebo.

reduction in PPG increments in pramlintide- but not placebo-treated patients in both A1C subgroups is illustrated by seven-point glucose profiles performed at baseline and week 16 (Fig. 3).

Safety

The most common adverse events were mild to moderate nausea (31% pramlintide, 10% placebo) and mild to moderate hypoglycemia (44% pramlintide, 47% placebo). Most nausea occurred within the first week of treatment and decreased over time. Two pramlintide-treated patients withdrew from the study due to mild or moderate nausea. Other adverse events leading to withdrawal were treatment-related pruritis at the injection site (one patient in each treatment arm) and alopecia, which was not considered treatment-related (one patient in the pramlintide arm). One event of severe hypoglycemia occurred in a pramlintide-treated patient who accidentally took a dose of rapid-acting insulin instead of insulin glargine. The investigator deemed this event unrelated to pramlintide treatment.

CONCLUSIONS — Patients with suboptimal glycemic control on basal insulin therapy may further improve control by increasing the basal insulin dose and/or adding mealtime insulin, but at the expense of additional weight gain and an increased risk of hypoglycemia (1,10). In addition to their clinical significance, these side effects are disliked by patients and, thus, may deter intensification of insulin therapy.

This study demonstrated that the addition of pramlintide with continued basal insulin titration allowed such patients to achieve improved glycemic control and additional metabolic benefits not achieved with insulin titration alone. Pramlintide, as an adjunct to basal insulin, allowed patients to achieve an A1C lower than that achieved with basal insulin titration alone. This was accomplished through pramlintide-dependent reductions in PPG increments coupled with reductions in fasting glucose resulting from basal insulin titration. Moreover, as in prior studies of pramlintide used in combination with mealtime insulin (16,17,19), this treatment regimen resulted in weight loss, while insulin titration alone caused weight gain. The coprimary composite study end point, comprising A1C, PPG, weight, and severe hypoglycemia components, was designed to measure the proportion of patients achieving a highly desirable clinical outcome. Significantly more pramlintide-treated patients achieved this end point (25%) than patients receiving insulin alone (7%), confirming the clinical advantages of pramlintide plus basal insulin over basal insulin alone.

Therapies that reduce PPG and body weight may provide long-term benefits to patients with type 2 diabetes. Postprandial hyperglycemia has been implicated in the development of micro- and macrovascular complications through mechanisms including increased oxidative stress and inflammation (20–22). Moreover, obesity is very common in patients with type 2 diabetes and contributes to an already-increased risk of cardiovascular disease.

Whether the severity of A1C elevation at baseline affects the benefits of adding pramlintide is of clinical interest. Therefore, ad hoc analyses were performed on patient subgroups with baseline A1C >8.5 or ≤8.5%. In patients with higher baseline A1C, basal insulin titration alone reduced A1C at the price of weight gain, while pramlintide plus basal insulin titration resulted in greater reductions in A1C (via PPG reductions) and induced weight loss. In patients with lower baseline A1C, basal insulin titration alone did not provide much benefit, indicating the need for additional therapy. In contrast, pramlintide plus basal insulin titration reduced both A1C and weight. Thus, pramlintide provided benefits beyond those of basal insulin alone regardless of baseline A1C.

This study had several limitations. First, the relatively short 16-week duration was not long enough to allow insulin dosage, A1C, and weight to plateau. Second, many patients entering this study had high A1C values despite substantial basal insulin doses (~54 units daily for those with baseline A1C >8.5%), suggesting that endogenous insulin secretion was low. Many of those patients will eventually need mealtime insulin to reach an A1C ≤7.0%. Studying the use of pramlintide with basal insulin earlier in the course of type 2 diabetes is therefore of

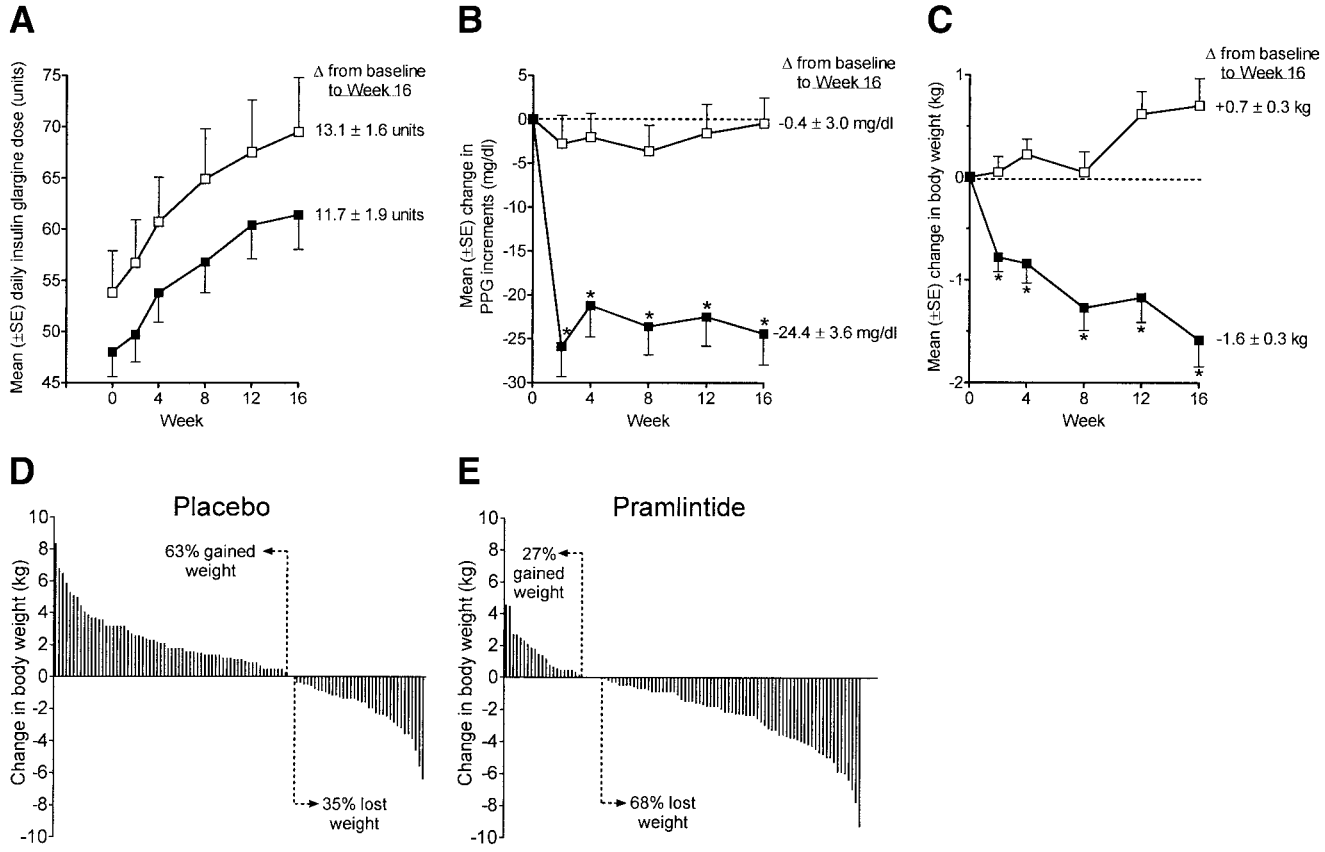

Figure 2—A: *Mean (±SE) daily insulin glargine doses.* □, *placebo;* ■, *pramlintide.* B: *Mean (±SE) change in PPG increments from baseline during the study.* □, *placebo;* ■, *pramlintide.* *P < *0.0001 for pramlintide vs. placebo.* C: *Mean (±SE) change in body weight from baseline during the study.* *P < *0.0001 for pramlintide vs. placebo.* □, *placebo;* ■, *pramlintide.* D *and* E: *Individual weight changes from baseline for placebo-treated* (D) *and pramlintide-treated* (E) *patients. Percentages of patients that gained or lost weight are indicated.*

interest. Third, the seven-point glucose profiles demonstrated improved but persistently high postbreakfast glucose increments in pramlintide-treated patients. Some pramlintide-treated patients might have benefited from mealtime insulin at breakfast to achieve adequate glycemic control.

Pramlintide added to basal insulin was generally well tolerated. Earlier studies of pramlintide indicated an increased risk of insulin-induced severe hypoglycemia, which occurred primarily in the more hypoglycemia-prone type 1 diabetic population (16,17). In contrast, no treatment-related severe hypoglycemia occurred in the present study. Also, the frequency of mild-to-moderate hypoglycemia was similar between the two treatment arms, despite the fact that pramlintide-treated patients achieved significantly better glycemic control.

In summary, adding pramlintide to basal insulin improved multiple aspects of diabetes control, thereby addressing important challenges associated with intensifying insulin therapy. These findings

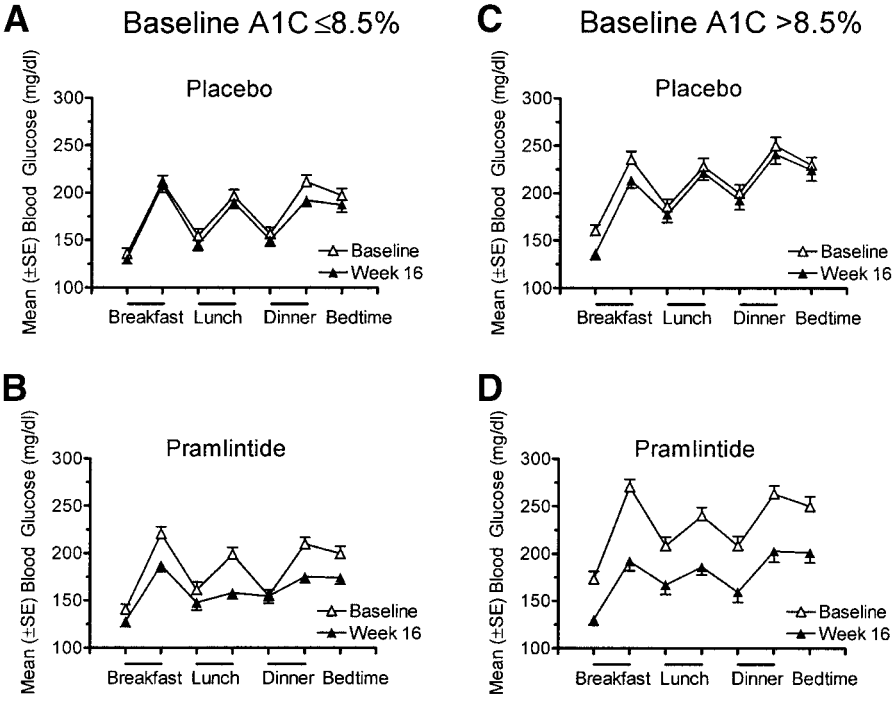

Figure 3—*Mean (±SE) seven-point glucose profiles in patients with baseline A1C ≤8.5%* (A *and* B) *or >8.5%* (C *and* D).

support pramlintide as a potential option for the next therapeutic step when patients with type 2 diabetes are not achieving glycemic targets with basal insulin therapy. Further studies examining pramlintide as an alternative to mealtime insulin are warranted.

Acknowledgments— Data from this study were presented at the 67th annual meeting of the American Diabetes Association, Chicago, Illinois, 22–26 June 2007, and at the 43rd annual meeting of the European Association for the Study of Diabetes, Amsterdam, the Netherlands, 17–21 September 2007.

APPENDIX

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