

# Pramlintide as an Adjunct to Basal Insulin: Effects on Glycemic Control and Weight in Patients with Type 2 Diabetes Mellitus

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## ABSTRACT

**Background:** Pramlintide is a synthetic analogue of the  $\beta$ -cell hormone amylin. When used as an adjunct to mealtime insulin, it reduces postprandial glucose concentrations, glycosylated hemoglobin (A1C) values, and weight. Due to its effects on postprandial glucose, pramlintide may also provide similar benefits when used as an adjunct to basal insulin in the absence of mealtime insulin in patients with type 2 diabetes mellitus (DM).

**Objective:** The current post hoc analyses examined the efficacy and tolerability of pramlintide as an adjunct to basal insulin in a subset of patients with type 2 DM in 2 clinical trials.

**Methods:** Post hoc analyses of 2 subgroups of patients with type 2 DM treated with pramlintide and basal insulin (with or without oral agents) with no mealtime insulin are reported. One subgroup of patients was from a 52-week, randomized, double-blind, placebo-controlled study; a second subgroup of patients was from an uncontrolled, open-label study. Mean (SE) changes from baseline in A1C, postprandial glucose, weight, and insulin dose are reported. Tolerability was also assessed.

**Results:** Baseline characteristics (mean [SD]) of the placebo-controlled study were as follows: pramlintide— $n = 18$ ; age, 59 (11) years; A1C, 9.4% (1.3%); weight, 88.4 (16.5) kg; body mass index (BMI), 31.8 (6.1) kg/m<sup>2</sup>; placebo— $n = 11$ ; age, 56 (9) years; A1C, 9.4% (1.6%); weight, 92.0 (13.4) kg; and BMI, 31.2 (5.1) kg/m<sup>2</sup>. Baseline characteristics (mean [SD]) of the patients from the open-label study were as follows:  $N = 10$ ; age, 60 (12) years; A1C, 8.1% (1.3%); weight, 109.2 (26.6) kg; and BMI, 35.7 (8.1) kg/m<sup>2</sup>. In the placebo-controlled study, pramlintide treatment (120  $\mu$ g BID) as an adjunct to basal insulin (neutral protamine Hagedorn, lente, or ultralente) resulted in mean (SE) reductions in A1C (pramlintide,  $-1.16\%$  [0.22%]; placebo,  $-0.48\%$  [0.18%];  $P < 0.05$ ) and weight (pramlintide,  $-2.3$  [1.0] kg; placebo,  $-0.9$  [1.0] kg) compared with placebo. Similarly, in the open-label study, pramlintide treatment (120  $\mu$ g before major meals) as an adjunct to insulin glargine resulted in mean (SE) reductions from baseline in A1C ( $-0.81\%$  [0.26%]; 95% CI,  $-1.40$  to  $-0.22$ ) and weight ( $-2.8$  [1.0] kg; 95% CI,  $-5.12$  to  $-0.47$ ). In addition, mean postprandial glucose excursions, ascertained by self-monitoring of blood glucose readings, were reduced after each meal. In both subgroups, pramlintide was generally well tolerated, and there were no episodes of severe hypoglycemia.

**Conclusion:** The improvements in glycemic control and weight in these post hoc analyses warrant further clinical investigation into the use of pramlintide as a potential next therapeutic step in patients with type 2 DM treated with basal insulin. (*Insulin*. 2007;2:166–172) Copyright © 2007 Excerpta Medica, Inc.

**Key words:** amylin, pramlintide, diabetes mellitus, insulin, hypoglycemia.

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## INTRODUCTION

Patients with type 2 diabetes mellitus (DM) suffer from chronic hyperglycemia as a result of peripheral insulin resistance coupled with progressive  $\beta$ -cell degeneration. The typical treatment course for patients with type 2 DM begins with medical nutrition therapy (MNT) and exercise, followed by the addition of oral antidiabetic drugs (OADs). Basal insulin is eventually required to improve fasting glucose control but does not adequately address postprandial hyperglycemia, and a mealtime insulin is subsequently indicated.<sup>1</sup> Unfortunately, intensification of insulin therapy with mealtime insulin, while improving postprandial glucose, frequently results in weight gain and increased risk of hypoglycemia.<sup>2</sup> For these reasons, patients and health care providers are often reluctant to add mealtime insulin to treatment regimens. Therapies that complement basal insulin to safely improve metabolic control without weight gain would provide a significant benefit to patients with type 2 DM.

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Pramlintide is a synthetic analogue of the  $\beta$ -cell hormone amylin. In patients with DM, it reduces postprandial glucose concentrations by regulating gastric emptying; prevents the inappropriate postprandial rise in plasma glucagon characteristic of DM; and increases satiety, resulting in reduced food intake.<sup>3</sup> In long-term, placebo-controlled clinical studies in patients with type 1 and type 2 DM,<sup>4-7</sup> pramlintide, used as an adjunct to mealtime insulin, improved patients' glycemic control and resulted in weight loss. Due to pramlintide's ability to lower postprandial glucose concentrations without weight gain, adding pramlintide to basal insulin may represent an alternative to mealtime insulin for treatment intensification. The current post hoc analyses examined the efficacy and tolerability of pramlintide as an adjunct to basal insulin in a subset of patients with type 2 DM in 2 clinical trials.<sup>4,8</sup>

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## MATERIALS AND METHODS

### Study Design

Primary outcome results of the first trial—a 52-week, randomized, double-blind, placebo-controlled clinical study

performed between 1996 and 1999 to examine the efficacy and safety of several pramlintide dosing regimens in insulin-using patients with type 2 DM—have been published previously.<sup>4</sup> Briefly, the study began with a 28-day placebo lead-in period followed by randomization to 1 of 4 dosing regimens: placebo TID or pramlintide 120  $\mu$ g BID, 90  $\mu$ g BID, or 60  $\mu$ g TID. Pramlintide was administered 15 minutes before major meals. Blinding was maintained by administering placebo at lunch to patients randomized to BID pramlintide dosing schedules (breakfast and dinner). Patients were encouraged to maintain their previous insulin and sulfonylurea or metformin regimens throughout the study to determine the additive effect of pramlintide. The current post hoc analysis included a subset of patients from the parent study using pramlintide at 120  $\mu$ g BID as an adjunct to basal insulin (neutral protamine Hagedorn [NPH], lente, or ultralente) without mealtime insulin, with or without OADs.

Primary outcome results from the second trial—an uncontrolled, open-label study performed between 2003 and 2005 to examine the efficacy and safety of pramlintide in patients with type 2 DM—have also been published previously.<sup>8</sup> Briefly, patients with type 2 DM initiated pramlintide at 120  $\mu$ g before major meals, concurrent with a proactive reduction of mealtime insulin doses (30%–50% reduction), to lower the risk of insulin-induced hypoglycemia. After establishment of pramlintide therapy, insulin doses were titrated based on self-monitoring of blood glucose (SMBG) to achieve individualized glycemic goals. Patients using metformin, a sulfonylurea, thiazolidinediones, or combinations thereof were instructed to continue their oral agents. The current post hoc analysis examined a subset of patients with type 2 DM using pramlintide (120  $\mu$ g) as an adjunct to basal insulin (insulin glargine) without mealtime insulin.

### Study Population

The placebo-controlled study included men and women aged  $\geq 18$  years with a clinical diagnosis of type 2 DM who had a glycosylated hemoglobin (A1C) level  $\geq 8.0\%$  at baseline and who had been on insulin therapy with or without OADs for  $\geq 6$  months. Patients were required to have had a stable insulin dose ( $\pm 10\%$ ) and stable weight ( $\pm 5$  kg) for  $\geq 2$  months before screening.

The open-label study included men and women  $\geq 18$  years old with a clinical diagnosis of type 2 DM who had an A1C level between 7.0% and 11.0% at baseline and who had been on insulin therapy with or without OADs for at least 6 months. Investigators were asked to select subjects who were unable to achieve adequate glycemic control despite insulin therapy.

In both studies, patients were excluded if they had a history of clinically significant thyroid, cardiac, hepatic, or renal disease, or either current or expected use of agents affecting gastrointestinal motility. Females were postmenopausal, surgically sterile, or using adequate contraception throughout the studies.

The study protocols were approved by the institutional review board of each study site or by a centralized institu-

tional review board. All patients provided written informed consent. These studies were conducted in accordance with the principles described in the Declaration of Helsinki (1964), including all amendments up to and including the South African revision (1996).

### Outcome Measures

In the post hoc analyses of these studies, efficacy end points included changes from baseline to 52 weeks in A1C, weight, and insulin dose. In the open-label study, changes from baseline to 52 weeks in patients' 7-point glucose profiles (obtained by SMBG values before and 1.5–2 hours after meals and at bedtime) were also examined.

Tolerability was assessed based on reports of adverse events, vital signs, physical examinations, responses to non-directed questioning, and clinical laboratory evaluations of all study participants during 52 weeks of treatment. As in the Diabetes Control and Complications Trial,<sup>9</sup> *severe hypoglycemic events* were defined as those requiring the assistance of another individual (including aid in the ingestion of an oral carbohydrate) and/or the administration of glucagon, IV glucose, or other medical intervention.

### Statistical Analysis

The placebo-controlled study subgroup included patients from the intent-to-treat (ITT) population who were using basal insulin (NPH, lente, or ultralente) without mealtime insulin and who had baseline and 52-week A1C measurements. Mean (SE) changes from baseline values were reported for all efficacy measures. A general linear model including treatment as covariate was used for between-group comparisons (placebo vs pramlintide), and significance was reported as *P* values.

The open-label study subgroup was defined as patients from the ITT population using insulin glargine without mealtime insulin and who had baseline and 52-week A1C measurements. Mean (SE) change from baseline values were reported for all efficacy measures for both groups. Postprandial glucose excursions were calculated from SMBG values and were defined as the postmeal blood glucose value (1.5–2 hours after meals) minus the premeal blood glucose value. Within-group comparisons of significance were reported as 95% CIs.

In both analyses, only patients who completed 52 weeks of therapy were included in the analysis (completer analysis). Therefore, the analysis did not include any patients who withdrew or who were lost to follow-up.

## RESULTS

### Baseline Characteristics

Characteristics of the post hoc study subgroups at baseline are shown in the **table**.<sup>4,8</sup> Patients in both study subgroups had suboptimal glycemic control and were obese at baseline. Patients in the placebo-controlled study subgroup used fewer OADs and less basal insulin than patients in the open-label study subgroup.

### Glycemic Control

In the placebo-controlled study subgroup, use of pramlintide as an adjunct to basal insulin resulted in significant, sustained reductions in mean (SE) A1C compared with use of placebo at 52 weeks (–1.16% [0.22%] vs –0.48% [0.18%]; *P* < 0.05) (**Figure**).<sup>4,8</sup> In the open-label study subgroup, 52 weeks of pramlintide treatment as an adjunct to basal insulin also resulted in a significant mean (SE) A1C reduction (–0.81% [0.26%]; 95% CI, –1.40 to –0.22) when compared with baseline. In the open-label study subgroup, mean (SE) fasting glucose was reduced at 52 weeks (129.0 [23.1] mg/dL) compared with baseline (139.0 [21.7] mg/dL). Furthermore, the mean (SE) postprandial glucose excursions were reduced from baseline by –38.2 (50.4) mg/dL at breakfast, –65.4 (24.3) mg/dL at lunch, and –33.6 (27.4) mg/dL at dinner. These reductions in postprandial glucose excursions resulted in mean (SE) postprandial glucose concentrations of 147.8 (14.7) mg/dL after breakfast, 152.3 (14.2) mg/dL after lunch, and 189.3 (18.4) mg/dL after dinner at 52 weeks.

### Weight

Pramlintide treatment as an adjunct to basal insulin in the placebo-controlled study subgroup resulted in a mean (SE) weight reduction from baseline of –2.3 (1.0) kg compared with –0.9 (1.0) kg in patients receiving placebo and basal insulin (**Figure**).<sup>4,8</sup>

In the open-label study subgroup, pramlintide treatment as an adjunct to basal insulin resulted in a significant mean (SE) weight reduction of –2.8 (1.0) kg (95% CI, –5.12 to –0.47) from baseline.

### Basal Insulin Use

Consistent with a study design that discouraged insulin dose adjustment, insulin doses in the placebo-controlled study subgroup were relatively stable over 52 weeks. Mean (SE) basal insulin dose for the pramlintide-treated patients decreased by –0.9% (5.6%) while it increased by 5.3% (6.8%) in patients receiving placebo.

In the open-label subgroup, where the study design allowed for insulin dose adjustment, the mean (SE) basal insulin dose decreased by –18.0% (10.0%).

### Tolerability

In both studies, pramlintide was generally well tolerated. Nausea (mostly mild to moderate in intensity) was a common adverse event in both subgroups (placebo-controlled study, 36.4% in the placebo group vs 33.3% in the pramlintide group; open-label study, 20.0%). There were no episodes of severe hypoglycemia in any subgroup. All hypoglycemia was mild to moderate in intensity and self-treated (1 of 18 pramlintide-treated patients in the placebo-controlled study and 3 of 10 patients in the open-label study reported hypoglycemic events).

## DISCUSSION

Basal insulin, which primarily affects fasting and preprandial blood glucose concentrations, is commonly introduced when

**Table.** Demographic and clinical characteristics of the post hoc study subgroups at baseline.\*

Baseline Characteristic	Placebo-Controlled Trial <sup>4</sup>		Open-Label Trial <sup>8</sup>
	Pramlintide (n = 18)	Placebo (n = 11)	Pramlintide (N = 10)
Age, y <sup>†</sup>	59 (11)	56 (9)	60 (12)
Sex, %			
Female	56	36	30
Male	44	64	70
Race, %			
White	56	73	80
Black	33	27	20
Hispanic	6	0	0
Other	6	0	0
Duration of diabetes mellitus, y <sup>†</sup>	11 (6)	11 (9)	11 (9)
A1C, % <sup>†</sup>	9.4 (1.3)	9.4 (1.6)	8.1 (1.3)
Weight, kg <sup>†</sup>	88.4 (16.5)	92.0 (13.4)	109.2 (26.6)
BMI, kg/m <sup>2†</sup>	31.8 ( 6.1)	31.2 (5.1)	35.7 (8.1)
Concomitant use of oral antidiabetic drugs, % <sup>‡</sup>			
Yes/no	22/78	46/54	90/10
Metformin	17	18	80
Sulfonylurea	11	27	30
Thiazolidinedione	0	0	40
Daily basal insulin dose, units <sup>†</sup>	48.9 (18.5)	45.7 (21.6)	77.2 (72.9)
Basal insulin type, %			
Insulin glargine	0	0	100
NPH	83	100	0
Lente	11	0	0
Ultralente	6	0	0

A1C = glycosylated hemoglobin; BMI = body mass index; NPH = neutral protamine Hagedorn.

\*Data presented as percentages may not equal 100 due to rounding.

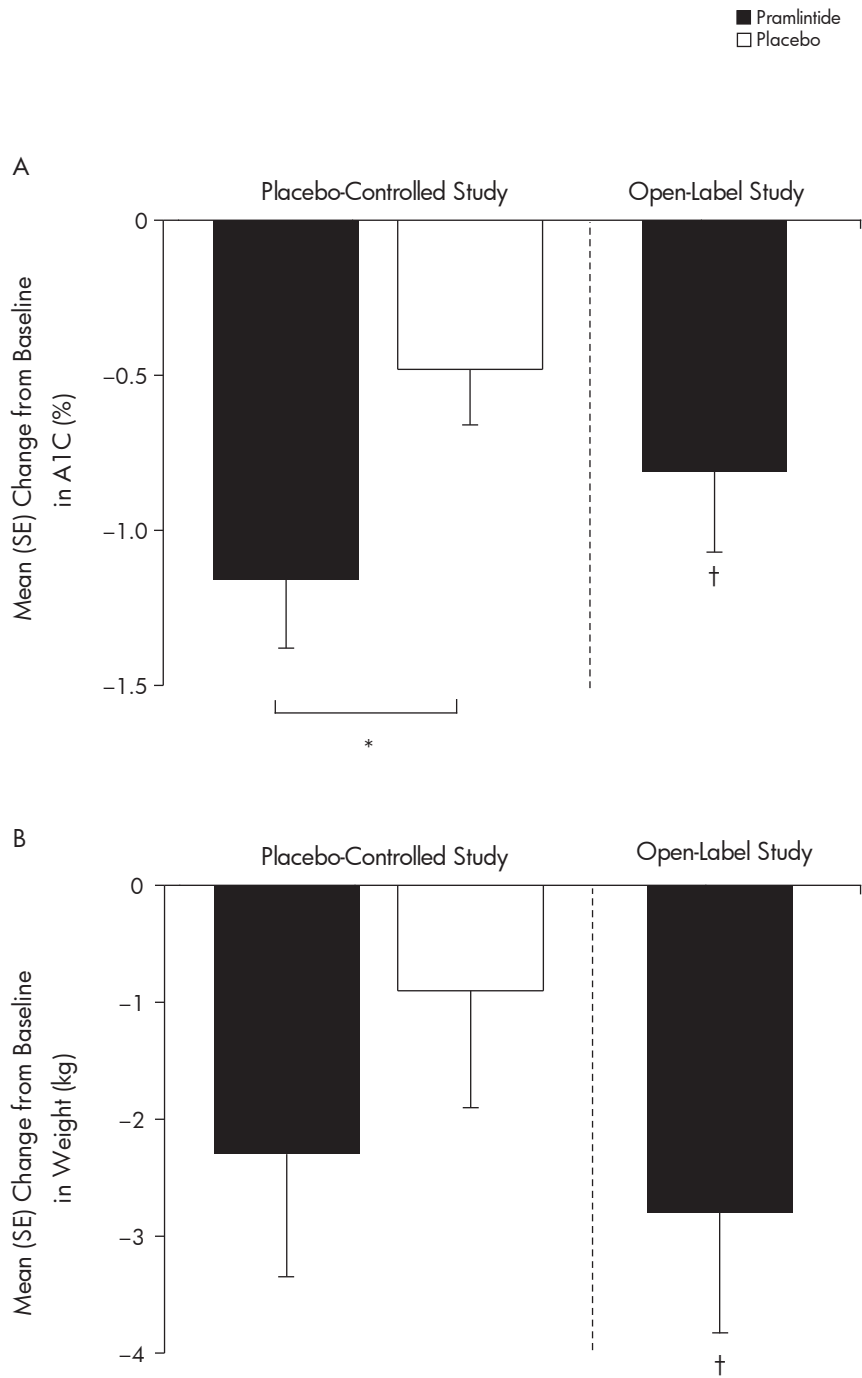
<sup>†</sup>Mean (SD).

<sup>‡</sup>Patients using medications in >1 category are counted for each category.

patients with type 2 DM are unable to maintain adequate glycemic control with OADs alone. Although aggressive titration of basal insulin can initially allow some patients to achieve adequate glycemic control, many patients eventually require the addition of mealtime insulin to address postprandial hyperglycemia.<sup>10</sup> Unfortunately, intensification of insulin therapy with mealtime insulin is associated with weight gain and an increased risk of hypoglycemia, both of which are significant deterrents for patients and health care providers. Pramlintide has been studied extensively as an adjunct to mealtime insulin in patients with type 1 and type 2 DM.<sup>4,6,7,11</sup> Due to its mechanisms of action, pramlintide may provide

significant clinical benefits—such as improved postprandial glucose control and weight loss—to patients treated with basal insulin in the absence of mealtime insulin.

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**Figure.** Mean (SE) change from baseline to 52 weeks in (A) glycosylated hemoglobin (A1C) and (B) weight for patients receiving either placebo or pramlintide in the placebo-controlled study<sup>4</sup> and pramlintide-treated patients in the open-label study.<sup>8</sup> In both A and B, the asterisk (\*) indicates significance of  $P < 0.05$  in the placebo versus pramlintide groups, determined by general linear model, and the dagger (†) denotes significance from baseline as 95% CIs for within-group comparisons.

The current analysis examined subgroups of patients with type 2 DM using pramlintide as an adjunct to basal insulin from 2 separate studies. In the placebo-controlled study,<sup>4</sup> insulin was maintained at a relatively stable dose. In the uncontrolled open-label study,<sup>8</sup> insulin doses were reduced on pramlintide initiation as determined by the individual investigator, then titrated based on SMBG after establishment of pramlintide therapy. Patients using pramlintide as an adjunct to basal insulin in both clinical scenarios experienced significant mean A1C reductions ( $-0.81\%$  [0.26%] in the open-label study and  $-1.16\%$  [0.22%] in the placebo-controlled study). Additionally, in the open-label study, SMBG concentrations indicated that mean postprandial glucose excursions were also reduced at each meal, resulting in a smoothed 7-point glucose profile. These improvements were achieved with no severe hypoglycemia. Pramlintide previously has been associated with an increased risk of insulin-induced severe hypoglycemia in patients using mealtime insulin, particularly those with type 1 DM.<sup>4,6,7,11</sup> In studies where mealtime insulin was proactively reduced on initiation of pramlintide, this risk was reduced.<sup>8,12</sup> In patients treated with basal insulin, pramlintide as an alternative to mealtime insulin may offer improved glycemic control with reduced risk of hypoglycemia. In the current analyses, the basal insulin dose remained relatively stable or decreased. Despite the differing study designs, it is conceivable that more aggressive titration of basal insulin to target fasting glucose concentrations in these pramlintide-treated patients may have resulted in even further improvement in overall glycemic control in both studies.

Even with implementation of MNT, improvement in glycemic control with insulin and most OADs (sulfonylurea, meglitinide, and thiazolidinedione) is often accompanied by weight gain.<sup>2,13–16</sup> Weight gain as a result of intensification of insulin therapy can be substantial and presents a barrier for patients, not only for aesthetic reasons but also due to the associated increase in cardiometabolic risk.<sup>2,13,15</sup> A previous study with pramlintide in 11 insulin-using patients with type 2 DM demonstrated an effect of increased satiety leading to decreased caloric intake at a buffet meal,<sup>17</sup> indicating that pramlintide

may uniquely augment the known benefits of MNT. In both the placebo-controlled and open-label study subgroups, patients treated with pramlintide experienced notable weight loss ( $-2.3$  [1.0] and  $-2.8$  [1.0] kg, respectively). It is possible that introduction of pramlintide as an adjunct to basal insulin may prevent or reduce the typical weight gain associated with intensified mealtime insulin and thereby improve patients' cardiometabolic risk profile. In addition, even moderate weight loss may encourage and motivate patients to maintain their MNT and exercise programs, which are the foundation of all type 2 DM treatment regimens.

It is possible that introduction of pramlintide as an adjunct to basal insulin may prevent or reduce the typical weight gain associated with intensified mealtime insulin and thereby improve patients' cardiometabolic risk profile.

## CONCLUSIONS

It is important to note that these subgroup analyses included only a small number of patients and should therefore be interpreted with caution. However, it is significant that in these 2 groups of patients with distinct baseline characteristics, similar improvements in glycemic control with weight loss were observed. These results suggest that pramlintide may be an alternative next step for patients unable to achieve glycemic targets using basal insulin therapy with or without OADs. Larger, long-term studies specifically designed to examine the efficacy and safety of pramlintide as an adjunct to basal insulin are warranted.

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