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

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Running Title: Pramlintide and basal insulin in T2 diabetes

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Abstract

**Objective** Assessment of 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/without oral antidiabetic agents (OAs) were randomized to addition of pramlintide (60 or 120 µg BID/TID) or placebo. Insulin glargine was adjusted targeting a fasting plasma glucose concentration 70-100 mg/dl. One co-primary endpoint was the change in A1C at Week 16. The other co-primary endpoint 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 endpoint.

**Results** More pramlintide- than placebo-treated patients achieved the composite endpoint (25% vs. 7%, P <0.001). Reductions (mean ± 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- vs. 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 not achieving glycemic targets with basal insulin ± OAs.

**Clinical trial registry number:** NCT00240253, clinicaltrials.gov
**Introduction**

Type 2 diabetes is characterized by insulin resistance and progressive beta-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 antidiabetic agents. 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 does 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 beta-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 oral antidiabetic agents.

**Research Design and Methods**

**Patients**

Enrolled patients were 25 to 75 years of age with type 2 diabetes and not achieving adequate glycemic control with insulin glargine (no mealtime insulin), with/without oral antidiabetic (OA) therapy (metformin, sulfonylurea [SFU] and/or thiazolidinedione [TZD]). Inclusion criteria at screening included A1C >7.0% and ≤10.5%, body mass index (BMI) 25-45 kg/m², insulin glargine treatment ≥3 months with a stable dose (±10%) ≥1 month and, if applicable, a stable dose of OAs ≥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 anti-obesity agents, or had a confirmed diagnosis of gastroparesis or any other significant medical condition.

The study protocol was approved by an institutional review board. All patients provided written informed consent prior to 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).

**Study design**

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 6 visits to the study site (baseline, 2, 4, 8, 12, 16 weeks). At the baseline visit, patients were randomized to receive pramlintide...
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(Amylin Pharmaceuticals, Inc., San Diego, CA) or placebo (Amylin Pharmaceuticals, Inc.). Randomization was stratified according to screening visit A1C (≤8% or >8%), BMI (≤35 kg/m² or >35 kg/m²), and SFU use (yes/no).

Study medication (pramlintide or placebo) was self-administered subcutaneously immediately prior to major meals depending on the patient’s typical meal pattern (BID or TID). Patients initiated study medication at a volume equivalent to 60 µg pramlintide/dose and escalated to a volume equivalent to 120 µg/dose within 3 to 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 targeting 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 prior to each visit consisting of measurements taken 15 minutes before and 1.5-2 hours 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 were 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 endpoints

Two co-primary endpoints were evaluated in this study. The first co-primary endpoint was the change in A1C from baseline to Week 16. The second co-primary endpoint was a dichotomous composite endpoint assessing the proportion of patients meeting all of the following pre-specified 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 endpoints included components of the composite endpoint, 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 endpoints 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 co-primary composite endpoint, and ~95% power to demonstrate non-inferiority of pramlintide vs. placebo for change in A1C from baseline. Non-inferiority for change in A1C was concluded if the upper limit of the two-sided 95% confidence interval (CI) for the difference between pramlintide and placebo was below the non-inferiority margin of 0.4%. The overall power for reaching both co-primary endpoints was expected to be ~85%. As both co-primary endpoints were required to be met, no adjustment to the significance level (α = 0.05) was required.
Analyses were performed on patients within the intent-to-treat (ITT) 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 (LOCF) approach for all efficacy analyses, with the exception of FPG, insulin dose, and the seven-point glucose profiles which were analyzed using the ITT observed population. Fisher’s exact test was used to compare the proportion of patients achieving the co-primary composite and secondary binary endpoints. A general linear model including treatment, baseline A1C stratum (≤8.0% or >8.0%), BMI stratum (≤35 kg/m² or >35 kg/m²), and SFU use (yes/no) as covariates was used to compare the change in A1C at Week 16. Parametric analyses of secondary continuous endpoints were performed using general linear models including treatment and baseline value as covariates. Descriptive analyses and P-values used the arithmetic and LS 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 prior to injection of study medication, resulting in an ITT 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.

**Co-primary endpoints**

**A1C.** A1C values progressively decreased throughout the study. Pramlintide-treated patients achieved a significantly (P <0.05) greater reduction (mean ± SE) from baseline at Week 16 (-0.70 ± 0.11%) than placebo-treated patients (-0.36 ± 0.08%), exceeding the non-inferiority criterion (upper limit of 95% CI = -0.04%) (Fig. 1A). 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 endpoint.** At Week 16, significantly more pramlintide-treated patients achieved the composite endpoint than placebo-treated patients: 25% vs. 7%, P <0.001 (Fig. 1B).

**Secondary endpoints**

**Components of the composite endpoint.**

The percentage of pramlintide-treated vs. placebo-treated patients achieving an A1C ≤7.0% or an A1C reduction ≥0.5% was not significantly different (Fig. 1C). Significantly more pramlintide-treated patients achieved mean PPG increments ≤40 mg/dl (P <0.0001) and 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. 1D). 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. 2A). 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 28/105 (27%) pramlintide-treated and 33/106 (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-treated vs. placebo-treated patients: -24.4 ± 3.6 mg/dl (pramlintide) vs. -0.4 ± 3.0 mg/dl (placebo) (P <0.0001) (Fig. 2B).

**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; mean ± SE) (Fig. 2C). 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. 2D 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 mg/dl 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 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 (1 patient in each treatment arm) and alopecia, which was not considered treatment-related (1 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 co-primary composite study endpoint, 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 endpoint (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 interest. Third, the seven-point glucose profiles demonstrated improved but persistently high post-breakfast 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
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Pramlintide indicated an increased risk of insulin-induced severe hypoglycemia, which occurred primarily in the more hypoglycemia-prone type 1 diabetes 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 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.
Appendix

Participating investigators
References


Table 1 – *Patient disposition and baseline demographics*

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Baseline demographics

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Data are means ± SD unless otherwise indicated.

Abbreviations: ITT, intent to treat; BMI, body mass index; FPG, fasting plasma glucose; PPG, postprandial glucose; OA, oral antidiabetic agent; SFU, sulfonylurea
Figure legends

**Figure 1.** (A) Mean (±SE) change in A1C from baseline to each visit. * indicates P <0.05 for pramlintide vs. placebo.(B) Percentage of patients achieving the composite endpoint at Week 16. (C) Percentage of patients achieving each component within the composite endpoint at Week 16. (D) Percentage of patients achieving at least two components, not including severe hypoglycemia, within the composite endpoint at Week 16. (B-D) * indicates P <0.005 and ** indicates P <0.0001 for pramlintide vs. placebo.

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

**Figure 3.** Mean (±SE) seven-point glucose profiles in patients with baseline A1C ≤8.5% (A and B) or >8.5% (C and D).
Figure 1

A

\[ \text{Mean (±SE) change in A1C (%)} \]

\[ \Delta \text{ from baseline to Week 16} \]

-0.36 ± 0.08%

-0.70 ± 0.11%

Week

0 4 8 12 16

B

Patients achieving composite endpoint (%)

Placebo 7%

Pramlintide 25%

C

Patients achieving components (%)

Placebo 45% 25% 37% 100%

Pramlintide 54% 64% 73% 90%

A1C ≤7% or reduction ≥0.5%

PPG increments ≤40 mg/dL

No weight gain

No severe hypoglycemia

D

Patients achieving components (%)

Placebo 15% 32% 18% 9%

Pramlintide 32% 44% 45% 45%
Figure 2

A. Mean (±SE) daily midling dose of insulin (units) over 16 weeks. Placebo group initiated with 13.1 ± 1.6 units and Pramlintide group initiated with 11.7 ± 1.9 units.

B. Mean (±SE) change in PPG increments (mg/dl) from baseline to Week 16. Placebo group showed a decrease of -0.4 ± 3.0 mg/dl, while Pramlintide group showed a decrease of -24.4 ± 3.6 mg/dl.

C. Mean (±SE) change in body weight (kg) from baseline to Week 16. Placebo group gained +0.7 ± 0.3 kg, while Pramlintide group lost -1.6 ± 0.3 kg.

D. Placebo: 63% gained weight, 35% lost weight.

E. Pramlintide: 27% gained weight, 68% lost weight.
Figure 3

A: Baseline A1C ≤ 8.5%
   - Placebo

B: Baseline A1C > 8.5%
   - Placebo

C: Baseline A1C ≤ 8.5%
   - Pramlintide

D: Baseline A1C > 8.5%
   - Pramlintide