A Randomized Study and Open-Label Extension Evaluating the Long-Term Efficacy of Pramlintide as an Adjunct to Insulin Therapy in Type 1 Diabetes

OBJECTIVE — To assess the effect of mealtime amylin replacement with pramlintide on long-term glycemic and weight control in patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS — In a 52-week, double-blind, placebo-controlled, multicenter study, 480 patients with type 1 diabetes were randomized to receive pramlintide injections of placebo or 30 μg pramlintide q.i.d., in addition to existing insulin regimens. At week 20, pramlintide-treated patients were re-randomized to 30 or 60 μg pramlintide q.i.d. if decreases from baseline in HbA1c were <1% at week 13. Of the 342 patients who completed the 52-week study, 236 individuals (~70%) elected to participate in a 1-year open-label extension in which all patients received 30 or 60 μg pramlintide q.i.d.

RESULTS — Treatment with pramlintide led to a mean reduction in HbA1c of 0.67% from baseline to week 13 that was significantly (P < 0.0001) greater than the placebo reduction (0.16%), and a significant placebo-corrected treatment difference was sustained through week 52 (P = 0.0071). The greater HbA1c reduction was associated with an average weight loss, rather than weight gain, and was not accompanied by an increased overall event rate of severe hypoglycemia. In the open-label extension, mean HbA1c levels decreased rapidly in patients receiving pramlintide for the first time and remained at reduced levels in patients who continued pramlintide treatment. The most common adverse events reported by the pramlintide group were mild nausea and anorexia, which both occurred during the initial weeks of treatment and dissipated over time.

CONCLUSIONS — Mealtime pramlintide treatment as an adjunct to insulin improved long-term glycemic control without inducing weight gain or increasing the overall risk of severe hypoglycemia in patients with type 1 diabetes.

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improvement in postprandial glucose excursions was seen (17,19).

The aim of the present study was to assess the effect of pramlintide, as an adjunct therapy to insulin, on long-term glycemic and weight control in patients with type 1 diabetes.

**RESEARCH DESIGN AND METHODS**

**Study design**

In this multicenter (35 centers in the U.S.), double-blind, parallel-group study, 480 patients with type 1 diabetes were randomized to receive preprandial injections of either placebo or 30 μg pramlintide (Amylin Pharmaceuticals, San Diego, CA) with the three major meals and a bedtime snack (four times per day) in addition to their existing insulin therapy. Patients and study personnel were blinded with respect to HbA1c levels, and there were no restrictions on patients’ insulin use. At week 20, pramlintide-treated patients whose HbA1c values decreased by <1% from baseline to week 13 were re-randomized to either 30 or 60 μg pramlintide q.i.d., whereas those who achieved a decrease ≥1% in HbA1c over this interval continued with 30 μg pramlintide q.i.d. for the remainder of the study. Placebo-treated patients remained on placebo. Re-randomization was performed by an unblinded third party.

The study medication was to be self-administered by the patient into the subcutaneous tissue of the anterior abdominal wall within 15 min before the major meals (0.1 ml volume at breakfast, lunch, dinner, and a bedtime snack). The study medication and insulin were to be administered in separate syringes and at different injection sites. Glucose control was to be reviewed by the investigator at each visit, and adjustments could be made as deemed appropriate to the patient’s insulin regimen consistent with good medical practice. Patients were instructed to record their daily insulin regimen on diary cards for 7 days before baseline and at weeks 13, 26, and 52.

Patients who completed the 52-week double-blind study were eligible for entry into a 1-year multicenter (31 centers in the U.S.), open-label extension in which all patients received 30 μg pramlintide q.i.d. (weeks 52–104). At week 65, investigators had the option to increase a patient’s dose of pramlintide from 30 to 60 μg q.i.d. based on HbA1c levels and clinical judgment.

**Study population**

Patients were between 16 and 70 years of age, had a history of type 1 diabetes for at least 1 year, had a C-peptide concentration ≤1.0 ng/ml, had a baseline HbA1c value between 7 and 13%, had been free from symptoms of severe hypoglycemia or hyperglycemia for 2 weeks, and had not adjusted their daily insulin dose by more than ±10% for 1 week before the study. Women who were not surgically sterile or postmenopausal were to practice appropriate contraception. Patients were excluded if they had a clinically significant history or presence of ischemic heart disease, hypertension (blood pressure >150/95 mmHg), gastrointestinal disease (including diabetic gastroparesis), renal disease (serum creatinine ≥2.0 mg/dl), and unstable diabetic retinopathy. Further exclusion criteria included treatment with drugs known to affect gastrointestinal motility (e.g., erythromycin, metoclopramide, cisapride, cholestyramine, or colestipol) or glucose metabolism (e.g., thiazide diuretics, corticosteroids, bile sequestering resins, acarbose, or metformin).

All patients provided written informed consent before both the double-blind study and open-label extension. Study protocols were approved by the Institutional Review Board of each study site or by a centralized Institutional Review Board.

**Study end points**

The primary efficacy end point was the relative change in HbA1c from baseline to week 52. Other efficacy end points for the double-blind study were absolute changes in HbA1c and body weight from baseline to weeks 13, 26, and 52. Additional efficacy end points were the relative change from baseline in daily insulin use and the proportion of patients with a baseline HbA1c ≥7% and HbA1c ≥8% who, at any time during the 52-week study, achieved an HbA1c <7% and HbA1c <8%, respectively, consistent with the glycemic targets recommended by the American Diabetes Association (20). Changes in HbA1c and body weight from baseline (visit 1 of the double-blind study) to weeks 54, 56, 65, and 78 and each subsequent 13-week interval were measured in the open-label extension.

Safety evaluations were based on reports of adverse events in response to nondirected questioning, clinical laboratory evaluations (hematology, serum chemistry, urinalysis), vital signs (blood pressure and pulse rate), electrocardiography, physical examinations, and fasting lipid levels in all randomized patients. In accordance with the Diabetes Control and Complications Trial (DCCT) (6), severe hypoglycemic events were defined as those that required either the assistance of another individual, the administration of glucagon, or the administration of intravenous glucose and expressed as the event rate per patient year.

**Statistical methods**

A minimum sample size of 110 patients in each treatment group was calculated to provide 80% power to detect a difference of 0.5% in HbA1c values between treatment groups at a 0.05 significance level. The within-treatment standard deviation for the change in HbA1c was assumed to be 1.3%.

For the double-blind study (weeks 0–52), analyses were performed on the evaluable population (patients who completed 52 weeks of treatment). Because there were no differences in efficacy or safety outcomes between the 30- and 60-μg pramlintide dose groups (weeks 20–52), data from these two groups were pooled. Differences between the placebo and pramlintide groups in mean changes from baseline in HbA1c values (all time points) and body weight (weeks 13, 26, and 52) were analyzed using a two-way ANOVA with treatment and site as factors. Safety analyses for the double-blind period were performed on all randomized patients who received at least one dose of study medication (intent-to-treat [ITT] population). All statistical tests were two-tailed with a significance level of 0.05.

For the open-label extension (weeks 52–104), efficacy and safety analyses were both performed on the ITT population.

**RESULTS**

**Patient disposition and baseline demographics**

Of the 480 patients randomized into the double-blind study (ITT population), 71% (n = 342; 168 placebo and 174 pramlintide) completed 52 weeks of treatment (evaluable patients) (Table 1). The overall withdrawal rates were identi-
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Table 1—Study disposition and demographic characteristics for the ITT population

<table>
<thead>
<tr>
<th>Disposition</th>
<th>Double-blind study</th>
<th>Open-label extension</th>
</tr>
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<tr>
<td></td>
<td>n</td>
<td>%</td>
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<tr>
<td>ITT population</td>
<td>237</td>
<td>70.9</td>
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<tr>
<td>Withdrawals</td>
<td>69</td>
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<td>Adverse event</td>
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<tr>
<td>Noncompliance</td>
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<td>2.5</td>
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<tr>
<td>Withdrawal of consent</td>
<td>14</td>
<td>5.9</td>
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<tr>
<td>Other</td>
<td>17</td>
<td>7.2</td>
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<tr>
<td>Evaluable population</td>
<td>168</td>
<td>70.9</td>
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Demographic Characteristics at Baseline

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Pramlintide</th>
<th>Placebo*</th>
<th>Pramlintide*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: male/female (%)</td>
<td>55/45</td>
<td>55/45</td>
<td>56/44</td>
<td>59/41</td>
</tr>
<tr>
<td>Race: Caucasian/other (%)</td>
<td>92/8†</td>
<td>96/5†</td>
<td>95/6††</td>
<td>97/3</td>
</tr>
<tr>
<td>Age (years)</td>
<td>40.4 ± 12.1</td>
<td>40.3 ± 11.6</td>
<td>44.7 ± 11.7</td>
<td>42.7 ± 10.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75.6 ± 13.3</td>
<td>75.0 ± 13.8</td>
<td>77.1 ± 13.7</td>
<td>76.0 ± 13.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.8 ± 3.5</td>
<td>25.2 ± 3.3</td>
<td>26.3 ± 3.4</td>
<td>25.4 ± 3.3</td>
</tr>
<tr>
<td>HbAlc (%)</td>
<td>8.9 ± 1.5</td>
<td>8.7 ± 1.3</td>
<td>8.7 ± 1.3</td>
<td>8.3 ± 1.4</td>
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<tr>
<td>Duration of diabetes (years)</td>
<td>17.1 ± 10.5</td>
<td>16.5 ± 10.0</td>
<td></td>
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</tr>
</tbody>
</table>

Data are means ± SD unless otherwise indicated. *Group to which patients were randomized during the initial double-blind study; †percentages do not add up to 100 due to rounding.

Table 1: Study disposition and demographic characteristics for the ITT population

Change in body weight

Double-blind study (weeks 0–52). The greater improvement in mean HbAlc observed in the pramlintide group was accompanied by a sustained reduction in mean body weight, whereas patients in the placebo group had an increase in mean body weight (Fig. 1B). The change in body weight was significantly different between the two treatment groups from week 13 onward (Fig. 1B).

Open-label extension (weeks 52–104). Patients who received pramlintide for the first time, after having been treated with insulin alone for 52 weeks, showed a progressive reduction in mean body weight similar to that seen in patients who had been randomized to pramlintide treatment at the beginning of the double-blind study (Fig. 1A). Patients who continued pramlintide treatment for a second year maintained a reduction from the original baseline in mean HbAlc through week 104.

Change in HbAlc

Double-blind study (weeks 0–52). Pramlintide treatment led to a mean reduction in HbAlc of 0.67% from baseline to week 13, which was significantly (P < 0.0001) greater than the reduction in the placebo group (0.16%) (Fig. 1A). A significant placebo-corrected treatment difference in favor of pramlintide was sustained throughout week 26 (−0.58 vs. −0.18%, P = 0.0001) and week 52 (−0.39 vs. −0.12%, P = 0.0071). Furthermore, approximately twice the proportion of pramlintide-treated compared with placebo-treated patients achieved the American Diabetes Association recommended glycemic targets of HbAlc <7% (25.0 vs. 11.3%, P = 0.01, Fisher’s exact test), and a substantially greater proportion achieved HbAlc <8% (58.6 vs. 35.1%, P = 0.04, Fisher’s exact test) at one point during the double-blind study.

Change in daily insulin use

Double-blind study (weeks 0–52). The greater improvement in mean HbAlc in the pramlintide group was not attributable to an overall increase in daily insulin use. Over the course of the study, insulin use in the pramlintide group changed only slightly from baseline (+2.6% at week 26 and +2.3% at week 52), whereas it increased in the placebo group through week 26 before reaching a plateau (+9.5% at week 26 and +10.3% at week 52). The treatment differences were significant at week 26 (P = 0.0323) and week 52 (P = 0.0176).

Daily insulin use was not recorded during the open-label extension.

Severe hypoglycemia

Double-blind study (weeks 0–52). The rates of severe hypoglycemia were not increased in pramlintide-treated patients, despite the greater improvement in mean

cal between the placebo and pramlintide treatment groups (Table 1). Of those who completed the study, 69% (n = 236; 111 placebo and 125 pramlintide) elected to continue in the open-label extension.

Baseline demographic characteristics for both treatment groups in the double-blind study and open-label extension were well balanced with regard to sex, race, age, and baseline BMI, HbAlc values, and diabetes duration (Table 1).
HbA1c (Table 2). For the first 4 weeks of treatment, the severe hypoglycemia event rate was similar for both groups, despite the fact that HbA1c decreased more markedly in the pramlintide group than in the placebo group (Table 2, Fig. 1A). From week 4 onward, the severe hypoglycemia event rate decreased in both treatment groups and tended to be lower in the pramlintide group. This observation could not be explained by a higher overall withdrawal rate or withdrawal due to hypoglycemia in the pramlintide-treated patients. Detailed evaluation of individual data revealed one placebo-treated patient who reported >100 episodes of severe hypoglycemia. After exclusion of this outlier, the severe hypoglycemia event rate in the placebo group decreased to 1.04 ± 0.24 (weeks 0–4), to 0.84 ± 0.10 (weeks 4–26), and to 0.52 ± 0.08 (weeks 26–52).

Open-label extension (weeks 52–104).
In the open-label extension, the severe hypoglycemic event rate was 0.68 per patient-year for those receiving pramlintide for the first time, which was lower than the rate observed for the placebo group from weeks 26 to 52 of the double-blind study (Table 2). In the group who received pramlintide for a second year, the severe hypoglycemic event rate was 0.43 per patient-year, which was the same as that observed from weeks 26 to 52 of their first year of therapy.

Other safety evaluations
Double-blind study (weeks 0–52).
There was no evidence that pramlintide treatment was associated with cardiac, hepatic, or renal toxicity or drug-related idiosyncratic adverse events. There were no clinically relevant changes in laboratory tests, plasma lipid parameters, vital signs, electrocardiography, or findings on physical examination.

The only treatment-emergent adverse events with an incidence ≥10% and a twofold greater incidence among pramlintide-treated versus placebo-treated patients were nausea and anorexia (Table 2). Most of these events were mild or moderate in intensity (defined as not interfering with daily activities and not requiring therapeutic intervention), transient in nature, and tended to occur early in the course of treatment (within the first 2 weeks). Nausea was the most common reason for withdrawal from the study: 7.4% in the pramlintide group vs. 1.7% in the placebo group. However, there was no difference in overall withdrawal rate between treatment groups.

Open-label extension (weeks 52–104).
Follow-up of the treatment-emergent adverse events reported with pramlintide treatment in the double-blind study also
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Table 2—Incidence of severe hypoglycemia and treatment-emergent adverse events with an occurrence ≥10% and the incidence in the pramlintide group at least double that of the placebo group for the double-blind study (weeks 0–52)

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Total</th>
<th>Severe</th>
<th>Total</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>21.9</td>
<td>1.7</td>
<td>46.5</td>
<td>6.2</td>
</tr>
<tr>
<td>Anorexia§</td>
<td>2.1</td>
<td>0.0</td>
<td>17.7</td>
<td>2.5</td>
</tr>
<tr>
<td>Vomiting‖</td>
<td>8.0</td>
<td>0.4</td>
<td>11.5</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Data are % or means ± SEM. *Severe hypoglycemia event rate was calculated as the total number of events for all patients on a treatment regimen divided by the total number of patient-years of observation; †World Health Organization Adverse Reaction Terminology (WHOART); ‡Intensity classified by the investigator; §terms such as a “feeling of fullness” were classified as anorexia; ‖vomiting is included because it maybe related to nausea.

showed an increased incidence of nausea (40.5%) and anorexia (12.6%) for the group receiving pramlintide for the first time (former placebo group). Again, most of these events were mild or moderate in intensity, were transient in nature, and occurred early in the course of treatment. In the group who continued on pramlintide therapy for a second year, the incidence of nausea and anorexia was 14.4% and 1.6%, respectively.

For all efficacy and safety variables, results for the ITT population were similar to those for the evaluable population during the double-blind study (data not shown).

CONCLUSIONS — Type 1 diabetes is characterized as a bi-hormonal deficiency, that is, the absence of circulating insulin and amylin (2); however, insulin replacement therapy has been the only available treatment for this disease. Despite considerable advances in insulin chemistry, delivery, and pharmacology, only a small proportion of patients with type 1 diabetes achieve near-normoglycemia with insulin replacement alone (3). The increased risk of severe hypoglycemia (6) and undesired weight gain (7,8) that usually accompany glycemic improvements with insulin therapy represent major obstacles toward achieving satisfactory glycemic control. The results of the present study indicate that addition of pramlintide to existing insulin regimens in patients with type 1 diabetes leads to a significant and sustained reduction in HbA1c that is not accompanied by an increased risk of severe hypoglycemia or by undesired weight gain. Therefore, mealtime amylin replacement with pramlintide as an adjunct therapy to insulin represents a safe and efficacious means of improving glycemic and weight control in patients with type 1 diabetes.

Consistent with preclinical findings of the physiologic role of amylin in postprandial glucose homeostasis (9,10), previous clinical trials in patients with type 1 diabetes have shown that mealtime amylin replacement with pramlintide slows the rate of nutrient delivery from the stomach to the small intestine (15,16) and prevents an abnormal increase in glucagonemia after meals (17,18). Collectively, these effects result in a marked improvement in postprandial glycemic excursions compared with prandial injections of insulin alone (17, 19). All of these effects were achieved with pramlintide doses of 30 or 60 μg, which resulted in plasma pramlintide concentrations similar to the postprandial amylin levels seen in healthy subjects. This indicates that the glucose-lowering effect of pramlintide is attributable to restoration of a more normal amylin effect during the prandial period in patients with type 1 diabetes.

The results of the present study clearly show that pramlintide treatment results in a long-term improvement of overall glycemic control, as evidenced by a significant reduction in HbA1c. Although the placebo-corrected reduction in HbA1c was most pronounced at week 13, the effect of pramlintide treatment was still clearly apparent and highly significant at the end of the 52-week double-blind study. In keeping with the complementary effects of insulin and amylin in postprandial glucose control, the present study was conducted with an add-on design so that mealtime pramlintide injections were added to a patient’s existing insulin therapy. By regulating the influx of exogenous (meal-derived) and presumably endogenous (liver-derived) glucose into the circulation, pramlintide has a unique and novel mechanism of action that is distinct from insulin and its analogs, which have a key role in mediating the disposal of glucose from the circulation into peripheral tissues (9,10). To our knowledge, this is the first demonstration of an antihyperglycemic agent, other than insulin, that improves long-term glycemic control in patients with type 1 diabetes.

It is well documented from the DCCT that glycemic improvement with insulin alone is readily accompanied by an increased risk of severe hypoglycemia (6). In the present study, the improvement in glycemic control (greater reduction in HbA1c) with pramlintide was not associated with an increased event rate of severe hypoglycemia. This is consistent with pramlintide being an antihyperglycemic agent, as opposed to insulin, which is a hypoglycemic agent. The mechanisms underlying the lack of increase in severe hypoglycemia with pramlintide are not yet fully established but may involve an increase in liver glycogen stores (21), a reduction in diurnal glucose fluctuations (22), and/or an improved hormonal counter-regulatory response to hypoglycemia (23). Of note, both preclinical studies (24,25) and studies in patients with type 1 diabetes (26) indicate that the effects of pramlintide on gastric emptying and glucagon secretion are overcome in the presence of insulin-induced hypoglycemia. Although pramlintide itself does not cause hypoglycemia, even at high
doses, it is important to consider that addition of pramlintide to insulin treatment may affect the risk of insulin-induced hypoglycemia. In the present study, investigators were allowed to adjust a patient’s insulin regimen consistent with good medical practices. Under this guidance, it was possible to improve long-term glycemic control without an increase in insulin use or an increase in overall risk of severe hypoglycemia in pramlintide-treated patients. This indicates that it may be prudent to initiate pramlintide therapy in conjunction with adequate glucose monitoring and judicious adjustments of insulin dosing.

Another well-documented, yet under-appreciated, side effect of glycemic improvement with insulin therapy in patients with type 1 diabetes is undesired weight gain. In both the Stockhol Diabetes Intervention Study (SDIS) (27) and the DCCT (7,8), patients with type 1 diabetes who were treated intensively with insulin experienced a significant increase in body weight (4–5 kg on average). Apparently, weight gain was most pronounced in patients who had the greatest improvement in glycemic control. Subsequent analyses of the DCCT data revealed the clinical significance of this weight gain, namely that the increase in body weight was associated with unfavorable effects on both lipid profile and blood pressure (8). Based on these findings, it is noteworthy that the glycemic improvement with pramlintide was not accompanied by increases in body weight, lipid levels, or blood pressure. Instead, adjunct therapy with pramlintide was associated with a mean reduction in body weight that was sustained for at least 1 year. Patients continuing pramlintide treatment during the open-label extension regained weight. Whether placebo patients would have continued to gain weight at the rate observed during the double-blind study is unknown, because these patients were switched to pramlintide treatment and subsequently showed a decrease in body weight. The lack of a placebo-control group in the open-label extension makes it difficult to determine whether the weight effect of originally pramlintide-treated patients was sustained during the second year. The weight-lowering effect of pramlintide observed in the double-blind study is consistent with evidence implicating amylin as a physiological postprandial satiety signal, involved in the central regulation of food intake and satiety (9,28). Amylin dose-dependently decreases food intake in rodents, mainly by reducing meal size and duration (28), whereas removal of endogenous amylin action via administration of a selective amylin antagonist increases feeding (29). Although the consequences, if any, of amylin deficiency on eating patterns in patients with type 1 diabetes are presently unknown, studies on the effect of pramlintide on satiety and dietary behavior in this patient population are now warranted.

Pramlintide therapy was generally well tolerated. There was no evidence of toxic adverse effects of pramlintide on any of the major organ systems, idiosyncratic side effects, or other serious safety concerns. In fact, the only treatment-emergent adverse events that had a >5 percentage point difference between the two treatment groups and were more common in pramlintide- than in placebo-treated patients were nausea and anorexia. In most cases, nausea and anorexia occurred within the first week of therapy, were of mild to moderate intensity, and began to resolve within days or weeks. Although the exact mechanism for these side effects is presently unknown, it is noteworthy that the area postrema is a crucial site of amylin (and by inference pramlintide) action and is also the location of the central chemoreceptor trigger zone for nausea and vomiting. Therefore, it is conceivable that the occurrence of nausea upon initiation of pramlintide therapy may be related to the sudden occupation of amylin receptors in the area postrema of patients with type 1 diabetes who had been completely deprived of circulating amylin for years. This raises the possibility that a gradual dose escalation at the initiation of pramlintide therapy may mitigate the occurrence of nausea, which is a notion that is currently being tested in clinical trials.

In conclusion, mealtime amylin replacement with pramlintide, as an adjunct to insulin therapy, improves long-term glycemic and weight control in patients with type 1 diabetes without increasing the risk of severe hypoglycemia.

Acknowledgments — We thank Tom Bicsak, Terrie Burrell, Alan Gottlieb, Erich Blase, and the Pramlintide-112 Clinical Study Group for their excellent assistance in the conduct, reporting, and quality control of the study.

APPENDIX

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