Randomized Comparison of Pramlintide or Mealtime Insulin Added to Basal Insulin Treatment for Patients With Type 2 Diabetes

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Objective: To compare the efficacy and safety of adding mealtime pramlintide or rapid-acting insulin analogues (RAIA) to basal insulin for patients with inadequately controlled type 2 diabetes.

Research design and methods: In a 24-week open-label, multicenter study, 113 patients were randomized 1:1 to addition of mealtime pramlintide (120 µg) or titrated RAIA to basal insulin and prior oral antihyperglycemic drugs (OAD). At screening, patients were insulin-naïve or on <50U/day basal insulin for <6 months. Basal insulin dosage was titrated from Day 1 seeking fasting plasma glucose (FPG) ≥ 70 mg/dL to <100mg/dL. Pramlintide and RAIA were initiated on Day 1 and Week 4, respectively. Proportion of patients achieving A1C ≤ 7.0% without weight gain or severe hypoglycemia at Week 24 was the primary endpoint.

Results: More pramlintide- than RAIA-treated patients achieved the primary endpoint (30% vs. 11%, p=0.018) on a similar dose of basal insulin. Pramlintide and RAIA yielded similar mean (±SE) values for FPG and A1C at 24 weeks (122±7 vs. 123±5 mg/dL; 7.2±0.2 vs. 7.0±0.1%) and similar least-squares mean reductions from baseline to endpoint (−31±6 vs. −34±6 mg/dL;−1.1±0.2% vs. −1.3±0.2%). RAIA but not pramlintide caused weight gain (+4.7±0.7kg vs. +0.0±0.7 kg; p<0.0001). Fewer patients reported mild to moderate hypoglycemia with pramlintide than RAIA (55% vs. 82%) but more patients reported nausea (21% vs. 0%). No severe hypoglycemia occurred in either group.

Conclusions: In patients taking basal insulin and OAD, premeal fixed-dose pramlintide improved glycemic control as effectively as titrated RAIA. The pramlintide regimen sometimes caused nausea but no weight gain and less hypoglycemia.

Abbreviations: FPG, fasting plasma glucose; ITT, intent to treat population; LOCF, last observation carried forward; LS, least squares; OAD, oral antihyperglycemic agents; PPG, postprandial glucose; RAIA, rapid-acting insulin analogue; T2DM, type 2 diabetes mellitus.

A table elsewhere in this issue shows conventional and Systeme International (SI) units and conversion factors for many substances.
A dding basal insulin therapy to oral agents improves glycemic control for many patients with type 2 diabetes (T2DM), but up to 50% of patients continue to have A1C values >7% (1–4). Persistent after-meal hyperglycemia is usually observed in such patients (6). The usual next step in treatment is addition of mealtime insulin injections, but this approach increases risks of weight gain and hypoglycemia (4, 6).

Previous studies have shown that defects in addition to insulin deficiency contribute to after-meal hyperglycemia. Both insulin and amylin are secreted by beta cells, and, in persons with abnormal beta-cell function, glucose- and mixed-meal-stimulated secretion of both hormones is delayed and reduced (7–9). Insulin deficiency impairs suppression of hepatic glucose production and enhancement of glucose uptake by tissues that normally limit post-meal hyperglycemia. Amylin deficiency accelerates gastric emptying, increases glucagon secretion, and alters satiety mechanisms (10, 11).

Pramlintide, an injectable synthetic analogue of amylin, slows gastric emptying, attenuates postprandial glucagon secretion, enhances satiety, and reduces food intake (12–14). Pramlintide is approved as adjunctive treatment for patients with diabetes who use mealtime insulin with or without oral anti-hyperglycemic drugs (OAD) and have not achieved desired glucose control. Recently, a 16-week, double-blind, placebo-controlled study of patients with T2DM showed that pramlintide reduces A1C and weight without increasing insulin-induced hypoglycemia when added to basal insulin ± OAD without mealtime insulin (15).

Pramlintide may offer an additional therapeutic option for mealtime use by patients with T2DM already using basal insulin. Rapid-acting insulin analogues and pramlintide have different mechanisms of action and different patterns of desired and unwanted effects. While both can limit after-meal hyperglycemia, RAIA often cause weight gain and hypoglycemia (6), whereas pramlintide is associated with weight loss and nausea (15, 16). This study was designed to compare the efficacy and side effects of pramlintide versus RAIA when added to basal insulin to intensify treatment of T2DM.

RESEARCH DESIGN AND METHODS

Study participants: Enrolled patients were 18-75 years of age, clinically diagnosed with T2DM, and had A1C>7% and ≤10% with or without use of any combination of metformin, thiazolidinedione, or sulfonylurea OADs. Study participants were pramlintide-naïve and either insulin-naïve or used <50 U/day of basal insulin for <6 months. Inclusion criteria included BMI ≥25 kg/m² and ≤50 kg/m². Female patients were neither pregnant nor lactating, and were postmenopausal or using birth control. Candidates were excluded if they adhered poorly to diabetes management recommendations, had recurrent severe hypoglycemia within the last 6 months, or had a history of hypoglycemia unawareness. Patients diagnosed with gastroparesis or who required medications altering gastric motility were excluded, as were patients using exenatide or sitagliptin, any antiobesity agents, systemic glucocorticoid agents, or investigational medications. Patients with eating disorders, history of bariatric surgery, or plans to lose weight were excluded, as were patients with any significant medical condition or advanced diabetes complications.

Ethical considerations: The study protocol was approved by applicable institutional review boards and conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before study initiation.

Study design and interventions: This was a randomized, open-label, parallel group, multi-center 24-week study conducted at 29 institutions.
centers throughout the United States between April 2007 and May 2008. After the screening visit, eligible patients visited the study center on Day 1 (baseline), and Weeks 4, 8, 12, 18, and 24. Scheduled telephone visits to review self-monitored glucose measurements and direct insulin adjustment occurred between visits. Randomization 1:1 to pramlintide (Amylin Pharmaceuticals, Inc., San Diego, CA) or RAIA (insulin lispro, insulin aspart, or insulin glulisine) occurred at baseline, and was centrally generated and stratified according to A1C screening values (≤9.0% or >9.0%) and insulin use (insulin-naïve or on basal insulin at screening).

All patients received insulin glargine or detemir throughout the study once or twice daily. Basal insulin was titrated at the investigator’s direction weekly or twice weekly to achieve a fasting plasma glucose (FPG) concentration of ≥70 mg/dL to <100 mg/dL, as in the Treat-To-Target Study (1). Study medication (pramlintide or RAIA) was self-administered subcutaneously (sc) before major meals. Patients in the pramlintide treatment group received 120 µg sc before major meals beginning Day 1 because a prior study demonstrated no increased risk of hypoglycemia when fixed-dose pramlintide was added to basal insulin (15). Dose reduction to 60 µg pramlintide per meal was permitted for patients with persistent clinically significant nausea. Patients randomized to RAIA received only titrated basal insulin therapy for 4 weeks to avoid the hypoglycemia risk associated with titrating basal insulin and RAIA simultaneously. After 4 weeks, RAIA-randomized patients started RAIA therapy with 5U lispro, aspart, or glulisine prior to each meal. Mealtime insulin doses were adjusted with investigator guidance by 1 to 2U every 3—7 days with the aim of maintaining glucose concentrations ≥70 mg/dL and <100 mg/dL prior to the subsequent meal or (for the dinnertime dose) at bedtime. Patients self-monitored blood glucose daily according to individualized advice from site investigators. A seven-point glucose profile consisting of measurements taken 15 minutes before and 1.5-2 h after the start of each of three meals and at bedtime was completed during the week prior to each visit. At each visit, weight, body circumference, and vital signs were measured and blood glucose values were reviewed. Participants were counseled on adjustment of basal and mealtime insulin dosage (RAIA group) at each visit. A1C was measured at all study visits, and FPG was measured at screening, baseline, and Weeks 4, 12, 24. No specific lifestyle modification was advised; patients were asked to maintain usual diet and exercise patterns.

**Study endpoints:** The primary endpoint was the proportion of patients achieving the following pre-specified criteria at Week 24: (1) A1C≤7.0%, (2) no weight gain from baseline, and (3) no severe hypoglycemia. Severe hypoglycemia was defined as an event requiring assistance of another individual and/or administration of glucagon injection or intravenous glucose. Secondary endpoints included the individual components of the composite endpoint, insulin dose, A1C, change in A1C, proportion of patients reaching A1C≤6.5%, FPG, postprandial glucose (PPG) increments, changes in weight, changes in waist circumference, and adverse events including the incidence, severity, and time courses of hypoglycemia and nausea.

**Statistical analyses:** A sample size of 45 patients per group was predicted to provide 90% power to detect a 27% difference in the proportion of patients achieving the primary endpoint (α=0.05). Analyses were performed on patients within the intent-to-treat (ITT) population including all randomized patients receiving at least one dose of study medication. Missing individual data were imputed from the last scheduled visit (last observation carried forward [LOCF]). Insulin
dose was analyzed in the ITT observed population. Measured values for insulin dose, A1C, FPG, and glucose increments were presented as arithmetic mean±SE.

Fisher’s exact test was used to compare the proportion of patients achieving the primary endpoint. The Cochran-Mantel-Haenszel test that controlled for A1C at screening was used as a confirmatory test. Inter-group comparisons of continuous changes from baseline were assessed with analysis of variance (ANOVA) models including treatment group, A1C at screening (≤9.0%, >9.0%), insulin treatment prior to screening, and baseline value (for parameters other than A1C). Data were reported as least-squares (LS) mean change±SE.

**RESULTS**

**Patient disposition, baseline demographics, and therapies:** Of 113 patients randomized, 48(84%) pramlintide-treated and 50(89%) RAIA-treated patients completed the study (Table 1). One patient in the pramlintide group withdrew consent before injecting study medication, resulting in an ITT population of 56 patients per treatment group. Baseline characteristics were well matched between groups (Table 1). Prior to the study, 46% of patients used insulin and 91% of patients used at least 1 OAD.

Basal insulin dosage increased steadily throughout the study resulting in similar mean doses at week 24: 52±4 U/day (0.48±0.04 U/kg/d) for pramlintide treated patients and 57±4 U/day (0.52±0.04 U/kg/d) for patients in the RAIA arm (Figure 1A). After 24 weeks, RAIA-treated patients administered a mean daily dose of 37±3 U (0.34±0.03 U/kg/d) of insulin lispro, aspart, or glulisine. Numbers of patients initiating therapy with insulin lispro, aspart or glulisine were 16(29%), 31(55%) and 9(16%), respectively. To achieve glycemic results similar to those of the pramlintide group, patients in the RAIA group used an average of 80% more insulin (basal+RA) at Week 24 (94 U vs. 52 U, respectively).

Forty-six participants (82%) remained on 120 µg pramlintide prior to meals throughout the study. Two participants reduced dosage to 60 µg due to nausea.

**Primary endpoint:** The primary composite endpoint comprised several highly desirable goals assessed after 24 weeks of treatment: A1C≤7.0%, no weight gain from baseline, and no severe hypoglycemia (Table 2). Significantly more pramlintide-treated than RAIA-treated patients achieved this endpoint (30% vs. 11%, p=0.018). Among the components of the composite, only the percentage of patients without weight gain at Week 24 differed significantly between pramlintide and RAIA-treated patients (59% vs. 16%, p<0.0001). No significant differences in the frequency of achieving A1C≤7.0% or in the incidence of severe hypoglycemia were observed between groups.

**Secondary endpoints:** A1C. Mean A1C at 24 weeks was 7.2±0.2 with addition of pramlintide and 7.0±0.1 with addition of RAIA (Figure 1B). The LS mean reduction of A1C from baseline was −1.1±0.2 for pramlintide and −1.3±0.2 for RAIA (p=0.46 between groups). A1C≤6.5% at 24 weeks was achieved by 16 of 56(29%) of patients treated with pramlintide and 19 of 56(34%) of patients treated with RAIA (p=0.68 between groups). A1C values were stable after Week 12 (Figure 1B).

**Weight and waist circumference:** A significant between-group difference in weight was observed throughout the study (Figure 1C). At Week 24, mean weights were 106±3 kg (pramlintide) vs. 109±3 kg (RAIA). LS mean changes in weight from baseline were +0.0±0.7 kg (pramlintide) vs. +4.7±0.7 kg (RAIA; p<0.0001).

Differences in waist measurements were consistent with weight differences. Waist circumferences at Week 24 were 115±2
cm and 120±2 cm for the pramlintide and RAIA groups, respectively. LS mean changes in waist circumference from baseline were −0.6±0.9 cm and +2.2±0.9 cm, respectively (p=0.016).

**Fasting plasma glucose:** Similar basal insulin titration in both treatment arms resulted in similar mean FPG concentrations at Week 24: 122±7 mg/dL (pramlintide) and 123±5 mg/dL (RAIA) (Figure 1D). The LS mean change of FPG from baseline was −31±6 mg/dL (pramlintide) and −34±6 mg/dL (RAIA; p=0.65). An FPG concentration <100 mg/dL was achieved at Week 24 by 17/56 (30%) of pramlintide-treated and 15/56 (27%) of RAIA-treated patients (p=0.83).

**Postprandial glucose increments:** Postprandial glucose increments were similar between treatment groups at Week 24 (Figure 2A). No significant difference in the LS mean change in postprandial increment from baseline to Week 24 was found between treatment groups (−17±5 mg/dL [pramlintide] vs. −27±5 mg/dL [RAIA], p=0.17).

**Adverse events:** The most common adverse events were hypoglycemia and nausea (Figure 2B).

Although no episodes of severe hypoglycemia were observed, mild or moderate hypoglycemia occurred more frequently than nausea in both treatment groups, and was observed in more patients treated with RAIA (82%) than with pramlintide (55%). Hypoglycemic events occurred more frequently in the pramlintide treatment group in the first 4 weeks, but were more common in the RAIA treatment group from 18 to 24 weeks (Figure 2C). Nausea was reported only in the pramlintide group (12/56 [21%]), most often early in treatment (10/56 patients in the first 4 weeks), and declined over time (Figure 2D). Two patients (4%) withdrew from pramlintide therapy and the study because of nausea.

Eight serious adverse events were reported in 6 patients during the study: one patient in the pramlintide group (coronary artery disease) and 5 patients in the RAIA group (coronary artery disease, congestive heart failure, ischemic cerebral infarction, syncope, non-cardiac chest pain, cellulitis, and biliary dyskinesia).

**CONCLUSIONS**

This head-to-head comparison demonstrated that premeal pramlintide and RAIA have similar glycemic effects when either agent is added to titrated basal insulin±OAD. On average, pramlintide reduced A1C from 8.2% to 7.2%, and RAIA reduced A1C from 8.3% to 7.0% after 24 weeks of treatment. Reductions in A1C, FPG, and post-meal glycemic increments were not statistically different between treatment groups. However, changes in body weight accompanying improved glycemic control differed between treatments. By the most conservative assessment (the between-treatment difference of change from baseline in all patients receiving study medication, LOCF), RAIA treatment contributed to a 4.7 kg (10.3 lb) gain compared to pramlintide treatment over 24 weeks. With similar glycemic effects and no severe hypoglycemic events with either treatment, the composite primary endpoint favored pramlintide over RAIA because of the difference in weight gain.

Other clinical differences between these therapies are related to unwanted effects. The incidence of hypoglycemia was greater with RAIA plus basal insulin than with pramlintide plus basal insulin, 82% versus 55%. Nausea occurred more frequently with pramlintide, and two patients (4%) withdrew from the study. However, as in other clinical studies, reports of nausea associated with pramlintide declined steadily during continued treatment.
This study builds on findings of a 16-week study that compared administration of pramlintide versus placebo during titration of basal insulin with continuation of OAD, in which glycemic control improved more with pramlintide than with placebo and no severe hypoglycemia was reported (15). Weight declined a mean of 1.6 kg with pramlintide but increased 0.7 kg with placebo. The larger absolute body weight difference between groups in this study is likely due to RAIA-associated weight gain.

The potential clinical importance of weight gain associated with treatment for hyperglycemia has been studied for many years, and remains controversial. An unfavorable relationship between adiposity and a variety of medical outcomes, including cardiovascular disease, is well established (17, 18). Recently, an observational study of ~4900 patients with T2DM showed a 13% increase in risk for fatal or non-fatal coronary heart disease with each 1-unit increase of BMI over ~6 years (19). Furthermore, evidence suggests that intended weight reduction reduces cardiovascular risk factors (20) and mortality (21). However, direct evidence that weight-gain associated with insulin treatment is harmful is lacking. Notably, at the end of 10 years of randomized treatment, the United Kingdom Prospective Diabetes Study (UKPDS) showed a marginally significant reduction of myocardial infarction (16%, p=0.052) with insulin or sulfonylurea treatment compared with dietary treatment, despite greater weight gain. Follow-up after cessation of randomized treatment showed persistence of the difference over time, and the advantage of insulin or sulfonylurea became statistically significant with more events (15%, p<0.01) (22, 23). Other findings indirectly suggest that avoiding weight-gain and hypoglycemia while improving glycemic control may provide cardiovascular benefit. In a study embedded in the UKPDS, treatment of obese patients with metformin, which is not associated with weight gain or hypoglycemia, reduced the incidences of myocardial infarction and all-cause mortality (23). Similar trends were shown in another study with acarbose, an antihyperglycemic agent which also does not cause weight gain or hypoglycemia (24). In contrast, the ACCORD Trial, which compared intensive versus standard glycemic control strategies associated with weight gain and hypoglycemia, was stopped early because of higher all-cause mortality in the intensive arm, despite a 1.1% lower A1C in this group (25). Potential underlying mechanisms include the doubled occurrence of weight gain >10 kg with intensive treatment, the three-fold increase of severe hypoglycemia, or both.

This study had several limitations. It was a small study, powered to address the composite primary outcome but not separate clinical outcomes, and the open-label design allows the possibility of unintended bias. The 4-week delay in initiating RAIA to avoid insulin-induced hypoglycemia from simultaneous initiation of basal and RA insulin was also a limitation. Because of the difference in the timing of RAIA initiation, the potential for weight gain in the RAIA group may be underestimated at Week 24, but glycemic outcomes at Week 24 did not seem to be affected, as insulin doses, A1C, and FPG in both treatment groups stabilized after 12 weeks, well before the study’s end. The incidence of nausea accompanying initiation of pramlintide (~20%) was confirmed as a leading drawback of starting treatment at 120 µg. Both nausea associated with pramlintide and hypoglycemia/weight-gain associated with RAIA might have been mitigated by more gradual titration. The small imbalance in use of detemir as the basal insulin (18 with pramlintide, 11 with RAIA) is of uncertain significance. Differences in overall costs between the pramlintide and RAIA regimens
might exist but are not addressed in this study of efficacy and safety.

Overall, these findings support the role of mealtime pramlintide as a potential alternative to RAIA for patients using basal insulin treatment with or without OAD who are not achieving glycemic goals. Longer-term studies to evaluate cardiovascular and microvascular outcomes of controlling after-meal hyperglycemia without weight gain and hypoglycemia would be helpful to inform clinical treatment decisions for patients with T2DM.

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REFERENCES
1. Riddle MC, Rosenstock J, Gerich J: The Treat to Target Trial: randomized addition of
glargine or human NPH to oral therapy of type 2 diabetic patients. *Diabetes Care* 26:3080-3086,
2003
2. Hermansen K, Davies M, Derezinski T, Ravn GM, Clauson P, Home P on behalf of the
Levemir Treat-to-Target Study Group: A 26-week, randomized, parallel, treat-to-target trial
comparing insulin detemir with NPH insulin as add-on therapy to oral glucose-lowering drugs in
week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as
add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetologia*
51:408-416, 2008
glaragine versus thrice-daily prandial insulin lispro in people with type 2 diabetes on oral
hypoglycemia agents (APOLLO): an open randomised controlled trial. *Lancet* 371:1073-1084,
2008
5. Janka HU, Plewe G, Riddle MC, Kliebe-Frisch C, Schweitzer MA, Yki-Jarvinen H:
Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial
treatment group: Addition of biphasic, prandial, or basal insulin to oral therapy in type 2
Woloszczuk W, Prager R: Basal and stimulated plasma levels of pancreatic amylin indicate its
9. Knowles NG, Landchild MA, Fujimoto WY, Kahn SE. Insulin and amylin release are both
diminished in first-degree relatives of subjects with type 2 diabetes. *Diabetes Care* 25:292-297,
2002
10. Gedulin BR, Jodka CM, Hermann K, Young AA: Role of endogenous amylin in glucagon
secretion and gastric emptying in rats demonstrated with the selective antagonist, AC187.
*Regulatory Peptides* 137:121-127, 2006
11. Lutz TA: Pancreatic amylin as a centrally acting satiating hormone. *Current Drug Targets*
6:181-189, 2005
human amylin analogue, pramlintide, corrects postprandial hyperglucagonemia in patients with
Effects of pramlintide, an amylin analogue, on gastric emptying in type 1 and 2 diabetes mellitus.
*Neurogastroenterol Mot* 14:123-131, 2002
Lush C, Weyer C, Horowitz M: Effect of pramlintide on satiety and food intake in obese subjects
Table 1: Patient disposition, and demographic and clinical characteristics at baseline

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<th>Disposition (n)</th>
<th>Pramlintide</th>
<th>RAIA</th>
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<tr>
<td>Randomized</td>
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<td>56</td>
</tr>
<tr>
<td>Withdrew prior to treatment</td>
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<tr>
<td>Completed</td>
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<td>50</td>
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<tr>
<td>Withdrew between treatment and Week 24</td>
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<td>6</td>
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<tr>
<td>Reason for withdrawal</td>
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<td>Withdrawal of consent</td>
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<td>Adverse event</td>
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<td>Lost to follow-up</td>
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<tr>
<td>Baseline demographics</td>
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<tr>
<td>Race (Caucasian/other) (n)</td>
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<td>Age (years)</td>
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<tr>
<td>Weight (kg)</td>
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<td>BMI (kg/m²)</td>
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<td>36 ± 6</td>
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<td>Diabetes duration (years)</td>
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<td>A1C (%)</td>
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<td>FPG (mg/dL)</td>
<td>155 ± 40</td>
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<td>Oral antidiabetes medication (OAD) use at randomization (n)</td>
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<td>Average number of oral medications per patient</td>
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<td>Insulin use prior to randomization (n)</td>
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<td>Daily basal insulin dose at baseline (U/day ± SD)</td>
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Table 2: Primary endpoint

<table>
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<tr>
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<th>Pramlintide (N=56)</th>
<th>RAIA (N=56)</th>
<th>Fisher’s exact test</th>
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<tr>
<td>Patients achieving composite endpoint*</td>
<td>17 (30)</td>
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<td>Individual Endpoints</td>
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<tr>
<td>Patients achieving A1C ≤7.0% at Week 24</td>
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<td>34 (61)</td>
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<td>Patients with no weight gain at Week 24</td>
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<td>Incidence of severe hypoglycemia</td>
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<td>0 (0)</td>
<td>NS</td>
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*Composite endpoint: A1C ≤7.0% at Week 24 with no weight gain and no severe hypoglycemia

Figure 1.
Figure 2.