Sustained Weight Loss Following 12 Months Pramlintide Treatment as an Adjunct to Lifestyle Intervention in Obesity

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Objective- To assess long-term weight-loss efficacy and safety of pramlintide used at different dosing regimens and in conjunction with lifestyle intervention (LSI).

Research design and methods- In a 4-month, double-blind, placebo-controlled, dose-ranging study, 411 obese subjects were randomized to receive pramlintide (6 arms: 120, 240, 360 μg, BID/TID) or placebo in conjunction with a structured LSI program geared toward weight-loss. Of the 4-Mo evaluable subjects (N=270), 77% opted to continue pre-existing treatment during an 8-Mo single-blind extension (LSI geared toward weight maintenance).

Results- At Mo-4, mean weight-loss from baseline in the pramlintide arms ranged from 3.8±0.7 to 6.1±0.8 kg (2.8±0.8 kg with placebo). By Mo-12, initial 4-mo weight-loss was regained in the placebo group, but was maintained in all but the 120 BID group. Placebo-corrected weight-loss with 120 TID and 360 BID averaged 3.2±1.2 kg (3.1±1.1%) and 3.3±1.1 kg (3.1±1.0%), respectively, at Mo-4 (both P<0.01; 4-Mo Evaluable N=270) and 6.1±2.1 kg (5.6±2.1 %) and 7.2±2.3 kg (6.8±2.3%), respectively, at Mo-12 (both P<0.01; 12-Mo Evaluable N=146). At Mo-12, 40 and 43% of subjects treated with 120 TID and 360 BID, respectively, achieved ≥10% weight-loss (versus 12% for placebo). Nausea, the most common adverse event with pramlintide in the 4-mo study (9-29% pramlintide vs 2% placebo), was generally mild-to-moderate and occurred in <10% of subjects during the extension.

Conclusions- When used over 12-months as an adjunct to LSI, pramlintide treatment, with low dose TID or higher dose BID regimens, helped obese subjects achieve greater initial weight-loss and enhanced long-term maintenance of weight-loss.

NCT00112021 and NCT00189514—ClinicalTrials.gov
To date, efforts to develop obesity pharmacotherapies aimed at reducing food intake and body weight have largely focused on small molecule anorectics, an approach that has repeatedly been hampered by safety concerns (1). Peptide hormones originating from pancreas and gut regulate meal size and body weight by acting as short-term (episodic) signals (2). In contrast to small molecules, peptide hormones do not readily diffuse the blood-brain-barrier to penetrate the entire central nervous system. Moreover, they act by enhancing signaling through specific, naturally occurring pathways regulating food intake, as opposed to acting more generally on multiple neuronal processes; for example by altering synaptic concentrations of neurotransmitters. Based on these characteristics, peptide hormone therapeutics are potential alternatives to centrally-acting small molecule anorectics.

Amylin, a 37-amino acid β-cell hormone co-secreted with insulin in response to meals, reduces food intake and body weight in rodents and may fulfill the criteria for a peripheral satiation hormone (3-6). Pramlintide, a synthetic analog of human amylin, has been extensively studied as an anti-hyperglycemic treatment and is currently under investigation as a potential treatment for obesity.

In two studies in obese subjects, pramlintide (120-µg single doses or 180-µg three times a day (TID) prior to meals for 6-weeks) reduced *ad libitum* food intake (7,8). Compared to placebo, pramlintide significantly reduced 24-h caloric intake (~500-750 kcal), caloric intake at a highly palatable fast-food challenge (by ~20%) and improved control of eating, evidenced by a 45% reduction in binge-eating score (8).

Pramlintide’s weight effects in obese subjects were initially assessed in a 16-week, randomized, double-blind, placebo-controlled, non-forced dose-escalation study. In this study, in which 88% of subjects escalated to the maximum dose (240-µg TID), pramlintide induced a placebo-corrected reduction in weight of 3.7% (P<0.001), with 31% of pramlintide-treated subjects achieving ≥5% weight loss (versus 2% for placebo; P<0.001)(9). Although these findings established a solid proof-of-concept for the anti-obesity potential of pramlintide, the study was limited to 4 months, did not employ lifestyle intervention (LSI), and subjects were not randomly assigned to different pramlintide doses or dose frequencies.

In order to evaluate the weight-loss efficacy and safety of pramlintide 1) across a range of doses, 2) across different dose frequencies, 3) in conjunction with LSI and 4) over 1-year, we conducted a 4-month dose-ranging study (main study) evaluating 6 pramlintide arms (120-µg, 240-µg or 360-µg twice-daily (BID) or TID) in conjunction with lifestyle intervention (LSI) and then implemented a 8-month single-blind extension protocol where subjects continued their pre-assigned treatment.

**RESEARCH DESIGN AND METHODS**

**Main double-blind study:** This was a 4-month, multicenter (24 centers in the United States), randomized, double-blind, placebo-controlled, dose-ranging study. Following a one-week placebo lead-in, 411 obese subjects were randomized (1:6) to receive placebo TID or pramlintide (120-µg, 240-µg or 360-µg BID or TID) via subcutaneous injection 15 min prior to morning, midday, and evening meals in conjunction with LSI. To maintain dose-frequency blinding, pramlintide BID subjects received placebo prior to midday meals. Pramlintide was initiated at 120 µg, and increased in 120-µg increments every 2-weeks until the assigned maintenance dose was reached (See Online Appendix Figure 1,
which is available at http://care.diabetesjournals.org).

**Single-blind extension study:** Subjects who completed the 4 months without major protocol deviations (4-Mo Evaluable) were eligible to continue their pre-assigned treatment for 8 months during the single-blind extension. [Following the placebo-controlled 8-mo extension, pramlintide treatment was continued in some subjects for non-placebo controlled safety assessments, data not shown.]

**Lifestyle intervention (LSI) program:** All subjects participated in an individualized LSI program (based on LEARN (10)) that was administered by trained study site personnel. LEARN® is a commercially available program for weight management that encompasses diet, physical activity, and behavioural modifications and has been extensively utilized in pharmacological and non-pharmacological weight loss intervention studies (14). At the start of the double-blind study, subjects were provided with a lifestyle intervention program manual and a digital pedometer. While LEARN provided a flexible approach to LSI, subjects were in general encouraged to reduce their daily caloric intake by 500 kcal/day and increase their steps up to ~10,000 per day. At the start of the extension (Month 4), subjects received another program manual containing additional lessons, focused on maintaining the behavioural changes taught during the double-blind study. Individual lifestyle counselling sessions were conducted by study personnel trained on the use of the LEARN® program, and occurred at all scheduled study-site visits (Day 1 and Weeks 2, 4, 8, 12 of the double-blind extension and each month during the extension). Subjects were provided with self-monitoring forms and encouraged to keep diet and exercise records (these records were not collected as study data). At each visit, records were reviewed and subjects encouraged to persevere with the program. Counselling was standardized across study sites. LSI was geared toward weight loss during the main study, and toward weight maintenance during the extension.

**Study participants:** Subjects were obese (BMI ≥30 to ≤50 kg/m² for at least 1 y) non-diabetic males and females, age 18 to 70 y, with abdominal obesity (waist circumference: >102 cm (male); >88 cm (female))(11). Women were surgically sterile, postmenopausal, or practicing appropriate contraception. Other entry criteria included medically non-significant baseline clinical laboratory tests.

Exclusion criteria included clinically active cardiac disease, diabetes, poorly controlled hypertension (sitting blood pressure >160/95 mm Hg), hepatic disease, malignant disease within 5 years of screening, major depressive or psychotic disorders, eating disorders, gastrointestinal disorders, current enrollment in a weight-loss program, or use of excluded concomitant medications including steroids, anti-obesity, antipsychotic, antiepileptic, and certain antidepressant agents (including monoamine oxidase [MAO] inhibitors, bupropion, tricyclic antidepressants, and tetracyclic antidepressants). Subjects on stable doses of SSRI and SNRIs, except for sibutramine, were permitted to enroll.

The study protocol was approved by the Institutional Review Board of each study site or by a centralized Institutional Review Board. All patients provided written informed consent before the main study and extension. This study was conducted in accordance with the principles described in the Declaration of Helsinki (1964) including all amendments up to and including the 1996 South African revision.

**Study endpoints:** The primary endpoints of both the main double-blind study and single-blind extension were changes in body weight, safety, and tolerability.
Safety assessments included incidence and severity of treatment-emergent adverse events. Other safety parameters included evaluation of concomitant medications, physical examination findings, vital signs, electrocardiograms, and clinical laboratory measures.

**Statistical analysis:** For the main study, 280 subjects completing the study (57 subjects randomized to each treatment group) were considered sufficient to detect a significant difference of 2.2 kg (SD of ~3.4 kg) in mean body weight change from baseline to Mo-4 between the placebo and any pramlintide group with ~80% power at the 0.05 significance level.

The intent-to-treat (ITT) populations for both the main double-blind study and single-blind extension included all randomized subjects who received at least one injection of study medication within the respective protocols. The 4-Mo and 12-Mo Evaluable populations included all ITT subjects that remained in the study through Mo-4 and Mo-12 (or received study medication for ≥330 days), respectively, who did not begin treatment with any restricted concomitant medication and with acceptable study medication compliance.

Summaries of safety and tolerability were conducted separately for each study using the corresponding ITT population. Changes in body weight and waist were analyzed separately for each study using the corresponding ITT and Evaluable populations. Missing data for the ITT populations were imputed utilizing the last-observation-carried-forward (LOCF) method. LOCF was implemented separately for each study using the corresponding ITT population. Subgroup analyses were conducted by the occurrence of treatment-emergent nausea in the ITT population.

Changes from baseline in body weight were analyzed using a general linear model including factors for treatment group, study site, gender, baseline BMI stratum (<35, ≥35 to <40, ≥40 kg/m²), and baseline body weight as a covariate. P-values were based on the least-squares (LS) mean differences between each active treatment group and the pooled placebo group in the change from baseline to each visit. The percentage of Evaluable subjects achieving ≥5% weight loss from baseline to Mo-4 and ≥5% and ≥10% weight loss from baseline to Mo-12 was analyzed using Fisher’s Exact Test. For all analyses, a P-value <0.05 was considered statistically significant. Demographics data are presented as mean±SD. All other parameters are presented as mean±SE.

**RESULTS**

**Baseline characteristics and subject disposition—Double-blind study:** In the main double-blind study, 408 (ITT) of the 411 subjects randomized to treatment with placebo or to one of six different pramlintide arms started the study medication. Withdrawal rates were slightly lower for the pooled pramlintide group (31%) than for placebo (37%) (Table 1). Overall withdrawal rates and reasons for withdrawal were generally similar between all pramlintide treatment arms.

**Single-blind extension:** Of the eligible subjects (4-Mo Evaluable N=270), 77% opted to participate in the single-blind extension. By Mo-12, withdrawal rates were 26% for pramlintide- versus 37% for placebo-treated subjects (Table 1). Baseline characteristics of subjects participating in the single-blind extension were well-balanced across arms in each study (Table 1).

**Body weight and waist circumference—Double-blind study:** In the placebo group, weight loss at 4 months averaged 2.8±0.8 kg (Evaluable: 2.6±0.7%; ITT-LOCF: 1.8±0.5 kg; 1.6±0.5%) (Figure 1A, B). By comparison, weight loss from baseline to Mo-4 in the pramlintide treatment
arms ranged from 3.8±0.7 to 6.1±0.8 kg (Evaluable: 3.9±0.7 to 5.7±0.9%; ITT-LOCF: 2.8±0.5 to 4.7±0.7 kg; 2.9±0.5 to 4.3±0.6%). Pramlintide 120-µg TID and 360-µg BID/TID achieved statistically significant reductions in absolute body weight at Mo-4 versus placebo (Evaluable and ITT-LOCF; \( P < 0.05 \) for each). Within these arms, 44-47% of subjects (Evaluable) achieved ≥5% weight loss versus 28% of placebo-treated subjects. Reductions in weight appeared dose-dependent for the pramlintide BID arms but not the pramlintide TID arms (Figure 1).

Weight loss was accompanied by reductions in waist circumference with several pramlintide dose arms achieving statistical significance versus placebo (Online Appendix Table 1).

**Single-blind extension:** In the extension (12-Mo Evaluable N=146), initial weight loss was largely regained in the placebo group but maintained or continued in all but the pramlintide 120-µg BID arm (Figure 1A,B). Excluding 120-µg BID, weight loss from baseline to Mo-12 in the pramlintide arms ranged from 6.3±3.5 to 8.0±2.0 kg (Evaluable: 6.0±2.8 to 7.9±1.9%; ITT-LOCF: 6.1±2.4 to 6.8±1.4 kg; 5.5±2.0 to 6.6±1.3%) versus 0.8±1.3 kg (Evaluable: 1.1±1.3%; ITT-LOCF: 2.4±1.1 kg; 2.2±1.0%) with placebo. Pramlintide 120-µg TID, 240-µg TID, and 360-µg BID/TID achieved statistically significant weight loss versus placebo (12-Mo Evaluable and 12-Mo ITT-LOCF; \( P < 0.05 \))(Figure 1A,B). In these arms, 41-65% of pramlintide-treated subjects achieved ≥5% weight loss from baseline to Mo-12 (placebo 18%; Figure 2A). In the lowest doses from each dosing regimen achieving statistically significant absolute weight loss in the 4-Mo double-blind study, 40% and 43% of subjects receiving 120-µg TID and 360-µg BID achieved ≥10% weight loss at Mo-12 (placebo 12%)(Figure 2B). Similar to Mo-4, reductions in weight appeared dose-dependent for the pramlintide BID, but not TID, arms. Subjects treated with pramlintide 120-µg TID, 240-µg TID and 360-µg BID also experienced significant reductions in waist circumference versus placebo (\( P < 0.05 \)) (Online Appendix Table 1).

Despite close-to-normal mean baseline values for lipoprotein profiles and blood pressure in this obese but relatively healthy study population, fasting lipid concentrations and blood pressure trended toward improvements with pramlintide treatment (Online Appendix Table 1).

**Safety and Tolerability:** In this study, pramlintide treatment at doses up to 360-µg TID was generally well-tolerated and no novel safety concerns were identified.

In the 4-mo double-blind study, nausea was the only adverse event that occurred with ≥5% incidence in the pooled pramlintide-treatment group and more frequently than with placebo. The incidence of nausea ranged from 9% (240-µg TID) to 29% (360-µg TID) for the various pramlintide treatment arms versus 2% for placebo. Nausea was generally mild-to-moderate and decreased over time. There was one case of severe nausea (360-µg TID) and 12 withdrawals due to nausea (1 each for 120-µg BID/TID and 240-µg TID arms; 2 each for 240-µg BID and 360-µg BID arms; 5 in the 360-µg TID arm).

During the single-blind extension, the incidence of nausea ranged from 0-9% in the pramlintide treatment arms versus 0% for placebo (Online Appendix Table 2). There were no reports of severe nausea or withdrawals due to nausea. The most frequent adverse event in the extension was upper respiratory tract infection (11.5% in the pooled pramlintide-treatment group; 14.8% with placebo).

Weight loss was dissociated from nausea, as subjects who did not experience nausea during the study achieved similar reductions in body weight as the overall population (Online Appendix Figure 1).
CONCLUSIONS

Consistent with their objectives, the present study and extension provide important new insights into the safety and weight-loss efficacy of pramlintide over a range of doses and dose frequencies. Our findings show that pramlintide in conjunction with LSI induces weight loss that is durable up to 12 months.

**Dose range and frequency:** In previous obesity studies, pramlintide doses were 180-µg up to 240-µg TID (8,9). In the present study, we examined three TID dosing regimens: 120-µg (currently approved for patients with type 2 diabetes), 240-µg (maximum dose previously studied (9)) and 360-µg (not previously tested). All three TID doses were effective over 12 months, with 240- and 360-µg TID providing little additional benefit over 120-µg TID. In contrast to TID dosing regimens, a clear dose-response relationship was evident among BID regimens, whereby 120-µg BID was suboptimal and 360-µg BID elicited weight loss of a magnitude similar to the TID regimens. Thus, at higher doses, BID dosing appears to be a feasible pramlintide regimen for weight loss.

The aforementioned dose-ranging findings may be explained by pramlintide’s pharmacokinetic profile. Following injection, plasma pramlintide peaks at ~30 min and declines steadily thereafter (t1/2=50 min)(3). With TID dosing regimens, pramlintide is administered prior to each meal and mean weight loss was similar across TID arms suggesting that doses of 120 µg or higher provided sufficient pre-midday meal exposure across all doses studied. In contrast, pramlintide was not administered prior to midday meal in the BID arms, so higher morning doses were likely required to achieve sufficient lunchtime exposure.

With respect to dose-selection for future studies, our results indicate that adequate weight loss efficacy and safety can be achieved with both TID and BID regimens. While 120 µg TID is commensurate with the pramlintide dosing regimen currently approved for the treatment of type 2 diabetes (12), in the present study in obese subjects without diabetes, 360 µg BID emerged as an equally effective dose for weight loss. Although the incidence of nausea was slightly greater with 360 µg BID than with the lower 120 mg TID regimen, nausea was generally mild and transient and no other safety issues were identified at this higher dose.

**Lifestyle intervention:** In this study, pramlintide’s effect was evident when used in conjunction with structured LSI, which was important to establish since non-pharmacological treatments are a cornerstone of weight management and official treatment guidelines recommend that pharmacological agents be tested in combination with LSI (13),(14). Weight loss at 4-months achieved with the most effective pramlintide dose regimens plus LSI was more than twice that obtained with LSI alone (placebo).

Rather than choosing a specific, prescriptive low-calorie diet or exercise program, the present study utilized LEARN, a well-established and flexible program aimed at making gradual changes in lifestyle, including healthy eating and behavior modification. LEARN has been extensively studied in non-pharmacological and pharmacological intervention studies (10),(15).

**Durability of Weight Loss:** To obtain insights into the long-term safety and efficacy of pramlintide in obesity, we instituted an extension protocol to the 4-mo dose-ranging study. Rather than reassigning all subjects to open-label pramlintide, we chose to maintain a single-blind and continue all subjects on their pre-existing treatment, including placebo, so as to better understand the interaction between the drug effect and LSI over 12 months.
Consistent with clinical practice experience, the initial weight loss obtained with LSI alone (placebo) was not maintained but was followed by gradual weight regain. Unlike placebo, 4-mo weight loss was maintained over 12 months in all but the lowest pramlintide BID arm. This is consistent with findings from 1-y pramlintide diabetes studies, which also showed durable weight loss over 1 year (12,16,17).

Assessment of the durability of pramlintide-induced weight loss in the present study is limited by several factors. These include a relatively high attrition rate, a common, well-recognized problem in obesity pharmacotherapy studies (18), and the possibility of self-selection bias. Of note, subjects were not initially recruited for a long-term study and only ~77% and ~50% of the baseline Evaluable and ITT populations, respectively, entered into the extension. Nonetheless, the majority of subjects who entered into the extension completed 12 months of treatment. Moreover, all pramlintide arms that achieved significant weight loss at Mo-12 in the Evaluable population, also achieved significant, albeit more moderate, weight loss in the ITT-LOCF analysis.

Although the aforementioned factors, and differences in study designs, make it difficult to contextualize pramlintide’s long-term efficacy, it is noteworthy that the proportion of subjects achieving 5% and 10% weight loss at 1 year compares quite favorably to the results reported with oral weight loss medications (15,19,20).

Safety and tolerability: Attempts to reduce food intake and body weight with centrally acting small molecule anorectics have been repeatedly hampered by safety concerns (1). Although the present study with pramlintide included a relatively small number of subjects, no novel safety concerns were identified. This is consistent with the concept that peptide hormone therapeutics based on naturally occurring satiety/satiation signals may hold promise as an alternative to small-molecule anorectics and may be potential candidates for combination therapy. Nausea, the most common tolerability-related adverse event with pramlintide treatment, was mild and transient. As in previous studies (9), pramlintide-mediated weight loss was clearly dissociable from the occurrence of nausea.

Previous studies have suggested that amylin analogs, such as pramlintide, may be viable components of a combinatorial peptide approach to obesity treatment (21). In diet-induced obese (DIO) rats, amylin induced synergistic, fat-specific weight loss when co-administered with leptin, a long-term adiposity signal(22). In a recently published, 24-week translational clinical research study in overweight/obese subjects, combination treatment with pramlintide (360 μg BID) and recombinant human leptin (R-met-Hu-Leptin, metreleptin, 5 mg BID) resulted in 12.7% mean weight loss from enrollment, significantly more than treatment with pramlintide or metreleptin alone (8.1 and 8.4%, P<0.001)(22). Further development of a pramlintide/metreleptin combination product for obesity is currently underway.

In conclusion, although larger longer-term confirmatory studies are required to determine its efficacy and safety for weight loss, alone or in combination, clinical findings obtained to date support the potential of pramlintide as part of a novel, integrated neurohormonal approach for the management of obesity.

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APPENDIX
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Sustained weight loss with pramlintide

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Table 1. Baseline demographics for the ITT population and subject disposition

| Double-blind study | Placebo | 120 µg | 120 µg | 240 µg | 240 µg | 360 µg | 360 µg |
|--------------------|---------|--------|--------|--------|--------|--------|--------|
|                    | 43±11   | 120 µg | TID    | 46±12  | 120 µg | TID    | 44±14  |
| Sex, Female (%)    | 73      | 66±17/15/2 | 70/15/11/4 | 70/16/13/2 | 75/9/14/3 | 76/13/10/2 |
| Age (y)            | 47±12   | 37.5±5.0 | 37.7±5.1 | 37.3±4.9 | 37.8±5.5 | 37.7±4.6 |
| Race, C/B/H/O (%)  | 71/17/12/0 | 107.7±19.5 | 104.7±19.2 | 106.9±22.1 | 108.1±17.2 |
| Body weight (kg)   | 104.0±17.8 | 38.1±5.4 | 37.8±5.5 | 37.8±5.5 |
| BMI (kg/m²)        | 37.2±4.4 | 38.1±5.4 | 38.3±5.4 | 38.0±4.5 |
| Waist circumference (cm) | 37.7±5.1 | 37.8±5.5 | 37.8±5.5 | 37.8±5.5 |
| Sex, Female (%)    | 73      | 73     | 71     | 72     | 75     | 71     | 73     |
| Age (y)            | 47±12   | 46±12  | 45±14  | 44±14  | 44±12  | 46±13  |
| Race, C/B/H/O (%)  | 71/17/12/0 | 107.7±19.5 | 104.7±19.2 | 106.9±22.1 | 108.1±17.2 |
| Body weight (kg)   | 104.0±17.8 | 38.1±5.4 | 37.8±5.5 | 37.8±5.5 |
| BMI (kg/m²)        | 37.2±4.4 | 38.1±5.4 | 38.3±5.4 | 38.0±4.5 |
| Waist circumference (cm) | 37.7±5.1 | 37.8±5.5 | 37.8±5.5 | 37.8±5.5 |
| Withdrew           | 37%     | 32%    | 36%    | 37%    | 20%    | 32%    | 27%    |
| Withdrawal of consent | 19%    | 10%    | 12%    | 7%     | 4%     | 10%    | 2%     |
| Adverse event      | 0%      | 3%     | 7%     | 7%     | 5%     | 9%     | 16%    |
| Other              | 19%     | 19%    | 17%    | 22%    | 11%    | 14%    | 10%    |
| Completed 4-Mo (n) | 37      | 40     | 38     | 34     | 45     | 40     | 45     |
| 4-Mo ITT (n)       | 59      | 59     | 59     | 54     | 56     | 59     | 62     |
| 4-Mo Evaluable (n) | 36      | 38     | 38     | 32     | 45     | 39     | 42     |

| Single-blind extension* | Placebo | 120 µg | 120 µg | 240 µg | 240 µg | 360 µg | 360 µg |
|-------------------------|---------|--------|--------|--------|--------|--------|--------|
|                        | 45±11   | 48±10  | 44±14  | 46±13  | 44±13  | 47±12  |
| Race, C/B/H/O (%)       | 82/11/7/0 | 77/7/17/0 | 77/7/17/0 | 88/3/6/3 | 84/8/8/0 |
| Body weight (kg)        | 105.8±17.9 | 104.0±19.2 | 106.9±20.4 | 106.9±15.6 |
| BMI (kg/m²)             | 37.7±4.8 | 37.6±4.8 | 37.8±5.9 | 38.0±4.5 |
| Waist circumference (cm) | 113.1±14.3 | 115.2±12.2 | 116.2±16.0 | 115.3±13.7 | 114.5±10.7 |
| 12-Mo ITT (n)           | 27      | 28     | 29     | 25     | 30     | 32     | 38     |
| Withdrawed              | 37%     | 14%    | 14%    | 28%    | 17%    | 31%    | 47%    |
| Withdrawal of consent   | 26%     | 7%     | 10%    | 12%    | 10%    | 22%    | 34%    |
| Adverse event           | 0%      | 0%     | 0%     | 0%     | 0%     | 3%     | 3%     |
| Other                   | 11%     | 7%     | 3%     | 16%    | 7%     | 6%     | 11%    |
| Completed 12-Mo (n)     | 17      | 24     | 25     | 18     | 25     | 22     | 20     |
| 12-Mo Evaluable (n)     | 17      | 25     | 25     | 17     | 23     | 21     | 18     |

All data are Mean ± SD unless otherwise indicated. Numbers may not add up to 100% due to rounding; C/B/H/O = Caucasian/Black/Hispanic/Other; *Demographics for participants of single-blind extension at baseline and prior to starting the double-blind study.
Figure 1. Changes in body weight (kg) from baseline (month 0) for BID (A) and TID (B) dosing regimens. For the double-blind study, data are presented from months 0-4 for the 4-Mo Evaluable population (n=270). For the single-blind extension, data are presented from months 4-12 for the 12-Mo Evaluable population (n=146) and at 12 months for the 12-Mo ITT population (LOCF) (n=209). There are two data points for the 4-month assessment: one assessment for subjects ending the double-blind study and another for subjects entering the single-blind extension. White circles = placebo; Pramlintide: black triangles = 120 µg; white triangles = 240 µg; black circles = 360 µg. Mean±SE; *P <0.05; **P <0.01 for each pramlintide treatment group versus placebo. For clarity, only Month 4 and Month 12 significance for double-blind study and single-blind extension, respectively, are depicted in figures.

Figure 2. Proportion of 12-Mo Evaluable subjects that achieved ≥5% (A) and ≥10% (B) weight loss from baseline (month-0) to Mo-12. Changes in body weight from baseline (month-0) to Mo-12 for each 12-Mo Evaluable individual in the placebo (C), pramlintide 120-µg TID (D) and pramlintide 360-µg BID (E) treatment arms. *P <0.05 for each pramlintide treatment group versus placebo.
Sustained weight loss with pramlintide

A

B

C

D

E

Proportion of subjects ≥5% Weight Loss

Proportion of subjects ≥10% Weight Loss

Change in body weight at Mo-12 (%)