Sustained Weight Loss Following 12-Month 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 (six arms: 120, 240, and 360 μg b.i.d. and t.i.d.) or placebo in conjunction with a structured LSI program geared toward weight loss. Of the 4-month evaluable subjects ($n = 270$), 77% opted to continue preexisting treatment during an 8-month single-blind extension (LSI geared toward weight maintenance).

RESULTS — At month 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 month 12, initial 4-month weight loss was regained in the placebo group but was maintained in all but the 120-μg b.i.d. group. Placebo-corrected weight loss with 120 μg t.i.d. and 360 μg b.i.d. averaged 3.2 ± 1.2 kg (3.1 ± 1.1% body wt) and 3.3 ± 1.1 kg (3.1 ± 1.0% body wt), respectively, at month 4 (both $P < 0.01$; 4-month evaluable $n = 270$) and 6.1 ± 2.1 kg (5.6 ± 2.1% body wt) and 7.2 ± 2.3 kg (6.8 ± 2.3% body wt), respectively, at month 12 (both $P < 0.01$; 12-month evaluable $n = 146$). At month 12, 40 and 43% of subjects treated with 120 μg t.i.d. and 360 μg b.i.d., respectively, achieved ≥10% weight loss (vs. 12% for placebo). Nausea, the most common adverse event with pramlintide in the 4-month 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 three-times-daily or higher-dose two-times-daily regimens, helped obese subjects achieve greater initial weight loss and enhanced long-term maintenance of weight loss.

Diabetes Care **31:1816–1823, 2008**

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 that regulate 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 cosecreted 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 antihyperglycemic 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 t.i.d. before meals for 6-weeks) reduced ad libitum food intake (7,8). Compared with placebo, pramlintide significantly reduced 24-h caloric intake (by ~500–750 kcal) and 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, nonforced dose-escalation study. In this study, in which 88% of subjects escalated to the maximum dose (240 μg t.i.d.), 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 antiobesity potential of pramlintide, the study was limited to 4 months and did not employ lifestyle intervention (LSI), and subjects were not randomly assigned to different pramlintide doses or dose frequencies.

To evaluate the weight loss efficacy and safety of pramlintide across a range of doses, across different dose frequencies, in conjunction with LSI, and over 1 year, we conducted a 4-month dose-ranging study (main study) evaluating six pramlintide arms (120, 240, and 360 μg b.i.d. and t.i.d.) in conjunction with lifestyle intervention (LSI) and then implemented an 8-month single-blind extension protocol in which subjects continued their preassigned treatment.

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Received 4 January 2008 and accepted 13 June 2008.
Published ahead of print at http://care.diabetesjournals.org on 20 June 2008. DOI: 10.2337/dc08-0029. Clinical trial reg. nos. NCT00112021 and NCT00189514, clinicaltrials.gov.

RESEARCH DESIGN AND METHODS

Main double-blind study

This was a 4-month, multicenter (24 centers in the U.S.), randomized, double-blind, placebo-controlled, dose-ranging study. Following a 1-week placebo lead-in, 411 obese subjects were randomized (1:6) to receive placebo three times daily or pramlintide (120, 240, and 360 μg b.i.d. and t.i.d.) via subcutaneous injection 15 min before morning, midday, and evening meals in conjunction with LSI. To maintain dose-frequency blinding, subjects receiving pramlintide twice daily also received placebo before midday meals. Pramlintide was initiated at 120 μg and increased in 120 μg increments every 2 weeks until the assigned maintenance dose was reached (online appendix Fig. 1, available at http://dx.doi.org/10.2337/dc08-0029).

Single-blind extension study

Subjects who completed the 4 months without major protocol deviations (4-month evaluable) were eligible to continue their preassigned treatment for 8 months during the single-blind extension. Following the placebo-controlled 8-month extension, pramlintide treatment was continued in some subjects for non–placebo-controlled safety assessments (data not shown).

LSI program

All subjects participated in an individualized LSI program (based on LEARN [10]) administered by trained study site personnel. LEARN is a commercially available program for weight management that encompasses diet, physical activity, and behavioral modifications and has been extensively used in pharmacological and nonpharmacological 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 generally encouraged to reduce their 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 behavioral changes taught during the double-blind study. Individual lifestyle counseling sessions were conducted by study personnel trained in the use of the LEARN program and occurred at all scheduled study site visits (day 1 and weeks 2, 4, 8, and 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 (records not collected as study data). At each visit, records were reviewed and subjects were encouraged to continue with the program. Counseling 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 and ≤50 kg/m^2 for at least 1 year) nondiabetic men and women aged 18–70 years with abdominal obesity (waist circumference >102 cm for men and >88 cm for women) (11). Women were surgically sterile, postmenopausal, or practicing appropriate contraception. Other entry criteria included medically nonsignificant baseline clinical laboratory tests.

Exclusion criteria included clinically active cardiac disease, diabetes, poorly controlled hypertension (sitting blood pressure >160/95 mmHg), 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, and use of excluded concomitant medications including steroids and antiobesity, antipsychotic, antiepileptic, and certain antidepressant agents (including monoamine oxidase inhibitors, bupropion, tricyclic antidepressants, and tetracyclic antidepressants). Subjects on stable doses of selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors, 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 end points

The primary end points of both the main double-blind study and the 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 ± ~3.4 kg in mean ± SD body weight change from baseline to month 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 the single-blind extension included all randomized subjects who received at least one injection of study medication within the respective protocols. The 4- and 12-month evaluable populations included all ITT subjects who remained in the study through month 4 and month 12 (or received study medication for ≥330 days), respectively, who did not begin treatment with any restricted concomitant medication and who had acceptable with 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 circumference were analyzed separately for each study using the corresponding ITT and evaluable populations. Missing data for the ITT populations were imputed using 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 in body weight from baseline were analyzed using a general linear model including factors for treatment group, study site, sex, baseline BMI stratum (<35, ≥35 to <40, and ≥40 kg/m^2), and baseline body weight as covariates. *P* values were based on the least squares mean differences in the change from baseline to each visit between each active treatment group and the pooled placebo group. The percentage of evaluable subjects achieving ≥5% weight loss from baseline to month 4 and

Table 1—*Baseline demographics for the ITT population and subject disposition,* N = *349*

		Pramlintide					
	Placebo	120 μg b.i.d.	120 μg t.i.d.	240 μg b.i.d.	240 μg t.i.d.	360 μg b.i.d.	360 μg t.i.d.
Double-blind study							
Sex (% female)	73	73	71	72	75	71	73
Age (years)	47 ± 12	43 ± 11	46 ± 12	45 ± 14	44 ± 14	44 ± 12	46 ± 13
Race, W/B/H/O	71/17/12/0	61/24/15/0	66/17/15/2	70/15/11/4	70/16/13/2	75/9/14/3	76/13/10/2
Body weight (kg)	104.0 ± 17.8	105.1 ± 19.9	105.6 ± 18.0	107.7 ± 19.5	104.7 ± 19.2	106.9 ± 22.1	108.1 ± 17.2
BMI (kg/m^2)	37.2 ± 4.4	37.5 ± 5.0	37.7 ± 5.1	38.1 ± 5.4	37.2 ± 4.9	37.8 ± 5.5	37.7 ± 4.6
Waist circumference (cm)	112.9 ± 12.6	112.4 ± 15.0	114.2 ± 12.3	116.2 ± 15.2	114.7 ± 13.7	114.6 ± 14.3	114.6 ± 11.7
4-month ITT (*n*)	59	59	59	54	56	59	62
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 months (*n*)	37	40	38	34	45	40	45
4-month evaluable (*n*)	36	38	38	32	45	39	42
Single-blind extension*							
Sex (% female)	78	75	72	80	80	66	79
Age (years)	49 ± 11	45 ± 11	48 ± 10	44 ± 14	46 ± 13	44 ± 13	47 ± 12
Race, W/B/H/O	82/11/7/0	64/25/11/0	76/14/10/0	72/16/8/4	77/7/17/0	88/3/6/3	84/8/8/0
Body weight (kg)	105.8 ± 17.9	102.6 ± 16.3	106.4 ± 18.0	107.0 ± 21.1	104.0 ± 21.0	108.8 ± 20.4	106.9 ± 15.6
BMI (kg/m^2)	37.7 ± 4.8	37.1 ± 4.3	37.6 ± 4.8	38.1 ± 5.7	37.1 ± 4.8	37.8 ± 5.9	38.0 ± 4.5
Waist circumference (cm)	113.1 ± 14.3	110.3 ± 13.3	115.2 ± 12.2	116.2 ± 16.0	114.8 ± 14.9	115.3 ± 13.7	114.5 ± 10.7
12-month ITT (*n*)	27	28	29	25	30	32	38
Withdrew (%)	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 months (*n*)	17	24	25	18	25	22	20
12-month evaluable (*n*)	17	25	25	17	23	21	18

Data are means ± SD unless otherwise indicated. Numbers may not add up to 100% due to rounding. C/B/H/O = White/Black/Hispanic/other. *Demographics for participants of single-blind extension at baseline and prior to starting the double-blind study.

≥5% and ≥10% weight loss from baseline to month 12 was analyzed using Fisher's exact test. For all analyses, a P value <0.05 was considered statistically significant. Demographic data are presented as means ± 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 (the ITT population) of the 411 subjects randomized to placebo or one of six 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-month evaluable n = 270), 77% opted to participate in the single-blind extension. By month 12, withdrawal rates were 26% for pramlintide-treated versus 37% for placebo-administered 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%]) (Fig. 1*A* and *B*). By comparison, weight loss from baseline to month 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 at 120 μg t.i.d. and 360 μg b.i.d. and t.i.d. achieved statistically significant reductions in absolute body weight versus placebo at month 4 (evaluable and ITT-LOCF $P < 0.05$).

Within these arms, 44–47% of subjects (evaluable) achieved ≥5% weight loss versus 28% of placebo-administered subjects. Reductions in weight appeared dose dependent for the pramlintide twice-daily but not the pramlintide three-times-daily arms (Fig. 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-month evaluable $n = 146$), initial weight loss was largely regained in the placebo group but maintained or continued in all but the pramlintide 120 μg b.i.d. arm (Fig. 1*A* and B). Excluding 120 μg b.i.d., weight loss from baseline to month 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 t.i.d., 240 μg t.i.d., and 360 μg b.i.d. and t.i.d. achieved statistically significant weight loss versus placebo (12-month evaluable and 12-month ITT-LOCF $P < 0.05$) (Fig. 1*A* and *B*). In these arms, 41–65% of pramlintide-treated subjects achieved ≥5% weight loss from baseline to month 12 (placebo 18%) (Fig. 2*A*). In the lowest doses from each dosing regimen achieving statistically significant absolute weight loss in the 4-month double-blind study, 40 and 43% of subjects receiving 120 μg t.i.d. and 360 μg b.i.d. achieved ≥10% weight loss at month 12 (placebo 12%) (Fig. 2*B*). Similar to at month 4, reductions in weight appeared dose dependent for the pramlintide twice daily but not three times daily arms. Subjects treated with pramlintide 120 μg t.i.d., 240 μg t.i.d., and 360 μg b.i.d. 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 t.i.d. was generally well tolerated and no novel safety concerns were identified. In the 4-month double-blind study, nausea was the only adverse event that occurred in the pooled pramlintide treatment group with ≥5% incidence and more frequently than with placebo. The incidence of nausea ranged from 9% (240 μg t.i.d.) to 29% (360 μg t.i.d.) 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 t.i.d.) and 12 withdrawals due to nausea (1 each for 120 μg b.i.d. and t.i.d. and 240 μg t.i.d. arms, 2 each for 240 μg b.i.d. and 360 μg b.i.d. arms, and 5 in the 360 μg t.i.d. arm).

During the single-blind extension, the incidence of nausea ranged from 0 to 9% in the pramlintide treatment arms vsersus 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 and 14.8% with placebo). Weight loss was dissociated from nausea, as subjects who did not experience nausea during the study achieved reductions in body weight similar to those in the overall population (online appendix Fig. 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 to 240 μg t.i.d. (8,9). In the present study, we examined three three-times-daily 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 three-times-daily doses were effective over 12 months, with 240 and 360 μg t.i.d. providing little additional benefit over 120 μg t.i.d. In contrast to three-times-daily dosing regimens, a clear dose-response relationship was evident among twice-daily regimens, whereby 120 μg b.i.d. was suboptimal and 360 μg b.i.d. elicited weight loss of a magnitude similar to the three-times-daily regimens. Thus, at higher doses, twice-daily 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 ($t_{1/2}$ = 50 min) (3). With three-times-daily dosing regimens, pramlintide was administered before each meal and mean weight loss was similar across three-times-daily arms, suggesting that doses of 120 μg or higher provided sufficient premidday meal exposure across all doses studied. In contrast, pramlintide was not administered before the midday meal in the twice-daily arms, therefore 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 three-times- and twice-daily regimens. Although 120 μg t.i.d. 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 b.i.d. emerged as an equally effective dose for weight loss. Although the incidence of nausea was slightly greater with 360 μg b.i.d. than with the lower 120 μg t.i.d. regimen, nausea was generally mild and transient and no other safety issues were identified at this higher dose.

LSI

In this study, pramlintide's effect was evident when used in conjunction with structured LSI, which was important to establish because nonpharmacological 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 used 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 nonpharmacological and pharmacological intervention studies (10,15).

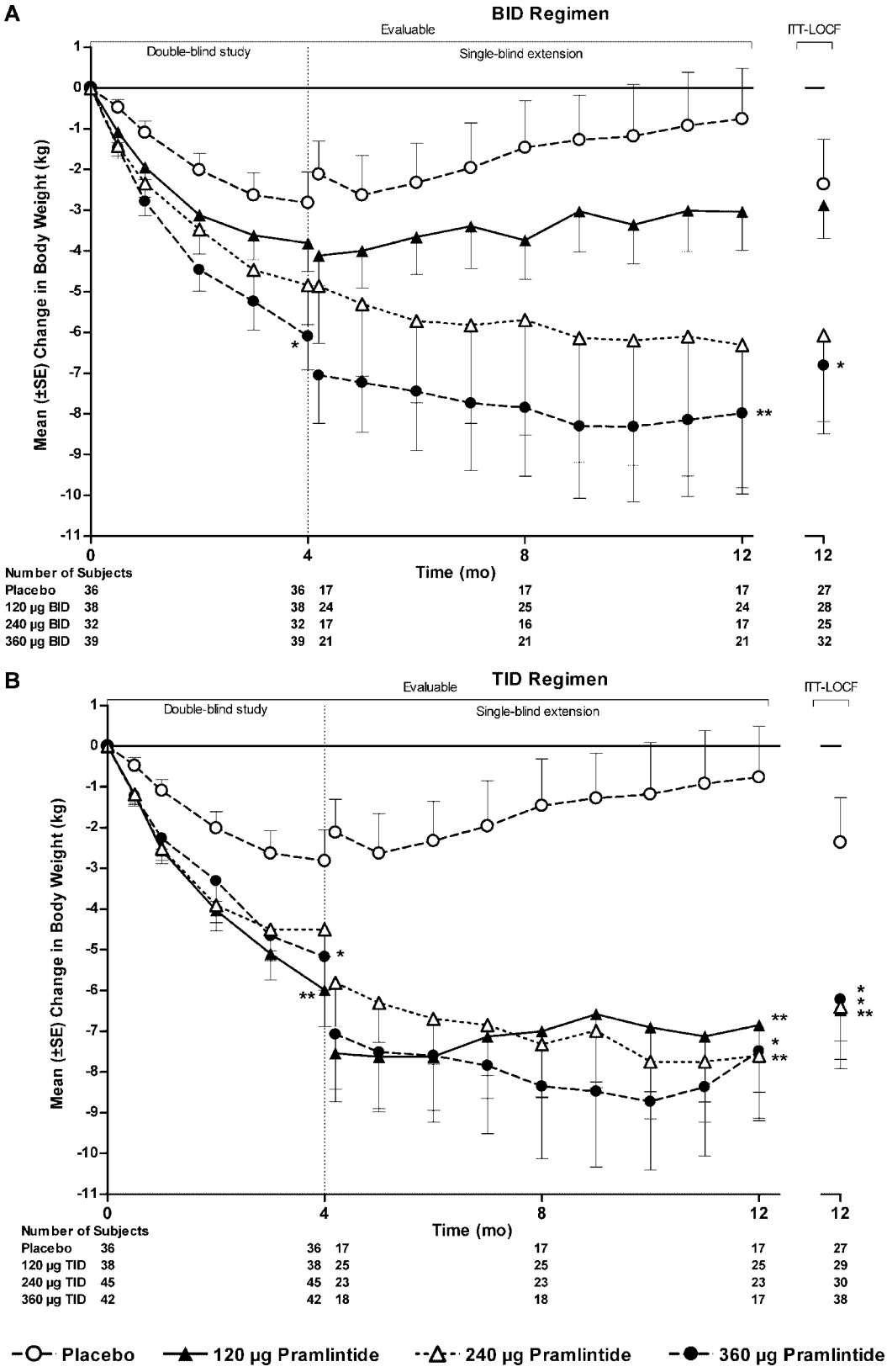

Figure 1—*Changes in body weight (kg) from baseline (month 0) for twice-daily* (A) *and three-times-daily* (B) *dosing regimens. For the double-blind study, data are presented from months 0–4 for the 4-month evaluable population* (n = *270). For the single-blind extension, data are presented from months 4–12 for the 12-month evaluable population* (n = *146) and at 12 months for the 12-month 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. For clarity, only month 4 and month 12 significance for double-blind study and single-blind extension, respectively, are depicted.* ○ = *placebo;* ▲ = *120 µg pramlintide;* △ = *240 µg pramlintide;* ● = *360 µg pramlintide. Data are mean ± SE.* *P < *0.05 and* **P < *0.01 for each pramlintide treatment group versus placebo.*

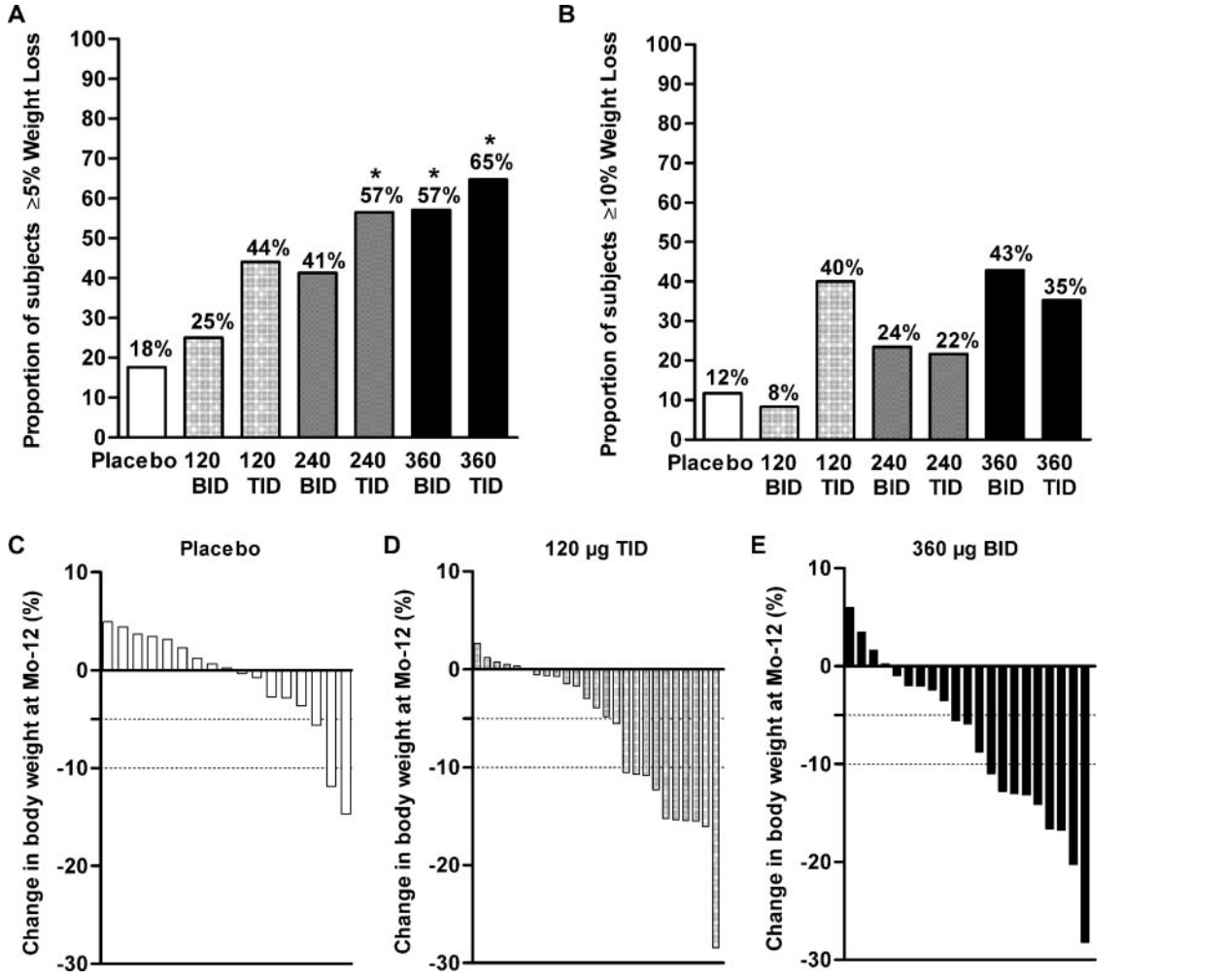

Figure 2—*Proportion of 12-month evaluable subjects who achieved ≥5% (*A*) and ≥10% (*B*) weight loss from baseline (month 0) to month 12. Changes in body weight from baseline (month 0) to month 12 for each 12-month evaluable individual in the placebo (*C*), pramlintide 120 µg t.i.d. (*D*), and pramlintide 360 µg b.i.d. (*E*) treatment arms. *P < 0.05 for each pramlintide treatment group versus placebo.*

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-month dose-ranging study. Rather than reassigning all subjects to open-label pramlintide, we chose to maintain a single-blind design and continue all subjects on their preexisting treatment, including placebo administration, 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-month weight loss was maintained over 12 months in all but the lowest pramlintide twice-daily arm. This is consistent with findings from 1-year 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 month 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 pre-

vious 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 rats, amylin induced synergistic, fat-specific weight loss when coadministered 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 b.i.d.) and recombinant human leptin (R-met-Hu-Leptin, meterleptin, 5 mg b.i.d.) resulted in 12.7% mean weight loss from enrollment, significantly more than treatment with pramlintide or meterleptin alone (8.1 and 8.4%, respectively; $P < 0.001$) (22). Further development of a pramlintide/meterleptin 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.

Acknowledgments— We are indebted to the subjects and investigators and to Shereen McIntyre, Jonathan Kornstein, Szecho Lin, Ya Huang, Rich Dopson, Lily Chen, Jackie Benson, and Christine Schulteis for their excellent assistance in the conduct, reporting, and quality control.

Some data from this study were presented at the 67th Annual Meeting of the American Diabetes Association, 22–26 June 2007, Chicago, Illinois; the 43rd Annual Meeting of the European Association for the Study of Diabetes, 17–21 September 2007, Amsterdam, the Netherlands; and NAASO, The Obesity Society Annual Scientific Meeting, 20–24 October 2007, Ernest N. Morial Convention Center, New Orleans, Louisiana.

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Participating centers: American Health Network; Big Sky Clinical Research; Capital Clinical Research Center; Comprehensive Weight Control Program; CSRA Partners in Health; Diabetes & Glandular Disease Research Associates; Diablo Clinical Research, Inc.; Henry Ford Health System; The Lindner Clinical Trial Center; Miami Research Associates; Pennington Biomedical Research Center; Philadelphia Health Associates; Profil Institute for Clinical Research, Inc.; Radiant Research Austin, Portland, Minneapolis, Kansas City, Chicago, and Salt Lake City-64th South; SAM Clinical Research; Scripps Clinic; University of Pennsylvania Weight & Eating Disorders Program; VA San Diego Healthcare System; and Washington University School of Medicine.

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