

Effect of bremelanotide on body weight of obese women: Data from two phase 1 randomized controlled trials

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Abstract

Aims: The melanocortin 4 receptor (MC4R) plays a central role in appetite regulation, and agonistic activity at this receptor promotes satiety. Results from two randomized controlled clinical trials examine the effects of bremelanotide's agonism at MC4R on caloric intake and body weight.

Methods: Premenopausal women with a body mass index >30 kg/m² were studied in two phase 1, single-centre, randomized, double-blind, placebo-controlled trials. Study A matched subjects 1:1 to receive subcutaneous placebo or bremelanotide three times daily for days 1-15. Study B was a crossover trial with six distinct treatment sequences consisting of three 4-day treatment periods, investigating once-a-day and twice-a-day exposure to bremelanotide versus placebo. Subjects received one of the three treatments twice-daily during each period: 0 mg/0 mg, 2.5 mg/0 mg or 2.5 mg/2.0 mg bremelanotide. Body weight and food intake were recorded in detail daily. Adverse events were recorded throughout both studies.

Results: In Study A, 27 of 30 bremelanotide subjects (90.0%) completed the trial and exhibited a significantly greater reduction in body weight after 16 days versus placebo [least squares mean difference (95% CI), -1.3 (-1.9 to -0.8) kg; $p < .0001$]. Mean caloric intake in bremelanotide subjects was decreased versus placebo, with a magnitude of reduction of approximately 400 kcal/day throughout Study A ($p < .01$). In Study B, 15 of 27 subjects (55.6%) completed all three phases. Significantly greater reduction of mean body weight occurred in twice-daily bremelanotide subjects versus placebo (1.7 vs. 0.9 kg, respectively, $p < .001$). Total caloric intake reduction was significantly greater in the bremelanotide groups versus placebo (mean difference range: 398-469 kcal; $p < .0001$).

Conclusions: Agonist activity at the MC4R may aid in reducing caloric intake and weight loss in obese women.

KEYWORDS

bremelanotide, MC4r agonist, melanocortin, obesity, weight loss

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1 | INTRODUCTION

Obesity, which is defined as a body mass index (BMI) ≥ 30 kg/m², represents a rising worldwide public health concern.¹ Obesity is associated with an increased risk of overall mortality and serious health conditions, including diabetes, coronary heart disease, stroke and certain cancers.¹ Health-related quality of life is significantly lower among adults with obesity, and obesity is associated with increased health care resource use and high economic burden.^{2,3} Safe and effective obesity treatments therefore remain a critical unmet need.

Genetic analysis has identified the melanocortin 4 receptor (MC4R) of the paraventricular nucleus of the hypothalamus as playing a central role in appetite regulation.⁴⁻⁶ Genetic mutations that inhibit signalling in the MC4R pathway lead to hyperphagia, decreased energy expenditure and early-onset obesity; such mutations have been identified as the cause of several rare genetic obesity disorders.⁴ Agouti-related peptide is an endogenous antagonist of the MC4R that works with neuropeptide Y to stimulate appetite, whereas MC4R agonists such as α - and β -melanocyte-stimulating hormone promote satiety.⁴ Agonism of the MC4R therefore represents an attractive target for potential obesity treatments. Bremelanotide is an MC4R agonist approved in the United States for the treatment of acquired, generalized hypoactive sexual desire disorder in premenopausal women.^{7,8} Given its role in MC4R agonism and that results showed a reduced food intake and body weight in both murine and rat models (Palatin Technologies, Inc. data on file), bremelanotide has the potential to be a treatment for human obesity.

Because of the mechanism of action, MC4R agonists may cause an increase in autonomic function resulting in elevated blood pressure values among its users – a potentially concerning adverse reaction in obese patients.⁹ The MC4R agonist setmelanotide was approved in 2020 for the treatment of certain rare genetic obesity disorders caused by mutations in the leptin/melanocortin signalling pathway.¹⁰⁻¹³

Here, we report results from two clinical studies evaluating the effects of bremelanotide on caloric intake and body weight in women with obesity. The primary goals were to show that targeted agonism of the MC4R could result in clinically meaningful weight loss, to determine sensitivity of effects to dosing, and to evaluate the short-term tolerability profile of MC4R agonism.

2 | METHODS

2.1 | Subjects

Study A enrolled white women aged 18-55 years with a BMI of 30-37 kg/m², and Study B enrolled women of any race aged 18-45 years with a BMI of 30-40 kg/m². For both studies, subjects remained at the research facility for the duration of the treatment periods. Inclusion criteria for both studies stipulated that participants be otherwise healthy and agree to use medically acceptable contraception for 3 months before and throughout the study. Key exclusion criteria for both studies included a hypertension diagnosis requiring medication or high blood pressure at screening; other health complications (e.g. diabetes, cardiovascular disease, neurological disease, renal

disease, endocrine disease or cancer); a psychiatric diagnosis requiring hospitalization or daily medication; a history of bariatric surgery; abnormal electrocardiogram or liver function test results; positive drug test results or a history of alcohol abuse within the past 6 months; participation in another study investigating an obesity agent within the past 3 months; an eating disorder, active attempt to lose weight, or body weight change of >5% within the past 3 months; smoking or smoking cessation treatment used within the past 3 months (Study A) or 1 month (Study B); and a change in medication within the past 30 days or planned during the study period.

2.2 | Ethics

The clinical study protocols, informed consent documents and any other appropriate study-related documents were reviewed and approved by an Independent Ethics Committee/Institutional Review Board, and both studies were conducted in full accordance with the Declaration of Helsinki; Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonization; good clinical practices as required by and described in 21 Code of Federal Regulations parts 50, 54, 56, 312 subpart D, and 314; and standard operating procedures for clinical investigation. All subjects gave informed consent.

2.3 | Study design

2.3.1 | Study A

Study A was a single-centre, randomized, double-blind, placebo-controlled phase 1 trial evaluating the safety, efficacy and tolerability of bremelanotide for weight loss. Subjects were randomly assigned 1:1 to receive either bremelanotide or placebo by subcutaneous (SC) injection (in the anterior thigh or abdomen) three times daily at 12:00, 16:00 and 20:00 h for 15 days. On day 1, subjects in the bremelanotide group received a 1.25-mg dose followed by two doses of 1.0 mg. On all subsequent days, subjects in this group received a 2.5-mg dose followed by two doses of 2.0 mg. Breakfast, lunch and dinner were served daily at approximately 9:00, 13:00 and 17:00 h, respectively, and subjects were permitted to snack as desired between 13:00 and 00:00 h (midnight). All food intake was optional except for breakfast, which subjects were requested to eat in its entirety. Intake was recorded including type of food eaten, portion weight before and after eating, and date and time of eating. The dosing schedule was based on a pharmacokinetic model and was designed to keep subjects in the therapeutic range while they had unrestricted access to food.

2.3.2 | Study B

Study B was a single-centre, randomized, double-blind, placebo-controlled phase 1 crossover trial evaluating the effects of one or two daily injections of SC bremelanotide on food intake given 1 h before breakfast and/or lunch. The study was divided into three treatment phases/regimens lasting 4 days each and separated by a 5-day

washout period; subjects were randomized to six different sequences dictating order of participation in the three dosing regimens. During regimen 1, subjects received twice-daily placebo injections; during regimen 2, subjects received daily injections of 2.5 mg followed by 2.0 mg bremelanotide; and during regimen 3, subjects received 2.5 mg bremelanotide followed by a placebo injection. All injections were delivered SC to the anterior thigh or abdomen 1 h before breakfast and 1 h before lunch. Breakfast, lunch and dinner were served daily, and subjects were permitted to snack as desired between 18:00 and 00:00 h (midnight). All food and beverage intake was recorded, including weight of the meal before and after consumption, the type of food eaten/beverage consumed along with the date and time of consumption. The dosing schedule for Study B was based on pharmacokinetic modelling designed to keep subjects within the therapeutic range of bremelanotide while having unrestricted access to food.

2.4 | Endpoints

2.4.1 | Study A

The efficacy endpoint of Study A was the mean change in body weight from baseline until the end of treatment on day 16. Body weight was recorded at screening and on each day throughout the study. Subjects were weighed in the morning between lavatory visit and breakfast, with a consistent, calibrated scale while wearing only underwear or scrubs. Blood pressure evaluation, a secondary objective of the study, was conducted at screening, on the 2 days before dosing, and on the day after dosing, as well as 15 min predose and 1 h postdose at all three doses throughout days 1-15.

2.4.2 | Study B

The primary endpoint of Study B was the mean daily caloric intake over the 4 days of treatment in each study phase. Secondary endpoints included caloric intake at each meal, change in body weight from baseline after each 4-day treatment phase, pharmacokinetic parameters of SC bremelanotide, and the occurrence of treatment-emergent adverse events (AEs). Subjects were weighed at screening and each morning throughout the study, between the lavatory visit and breakfast, using a consistent, calibrated scale while wearing only underwear or scrubs. Blood samples for pharmacokinetic analysis were collected at the following time points in reference to the first daily injection: day 1 of each treatment period 30 min predose and 30 min, 1, 2, 3.5, 4.5, 5, 6, 7.5, 9 and 11 h postdose; and day 4 of each treatment period 3.5 h postdose. Plasma concentrations were determined by high-performance chromatography/tandem mass spectrometry.

2.5 | Safety data collection

2.5.1 | Adverse events, vital signs, laboratory and physical examination

Treatment-emergent AEs including serious AEs (SAEs), changes in vital signs, electrocardiogram measurements, clinical laboratory results

(serum chemistry, haematology and urinalysis), and abnormal physical examination results were recorded throughout both studies.

2.5.2 | Blood pressure

Blood pressure was measured in both studies daily pre- and postdose, and subjects were withdrawn if they met prespecified criteria for blood pressure results. Patients were seated for at least 5 min before all blood pressure readings. To continue in the study, subjects were required to have systolic blood pressure <155 mmHg and diastolic blood pressure <95 mmHg at all assessments; if the average of three readings did not meet criteria, subjects were retested every 15 min for 1 h, and subjects were withdrawn if ≥ 2 consecutive assessments or ≥ 4 assessments within 24 h did not meet criteria.

2.6 | Analysis

2.6.1 | Study A

Efficacy in Study A was evaluated in the per-protocol population, which included all randomized subjects who received ≥ 1 dose of the study drug and who had ≥ 1 measurement of caloric intake or weight after the first dose, during which the subject was still considered per protocol. Missing values were not imputed. Mean within-subject change in body weight along with differences between treatments were calculated using an analysis of covariance model with baseline weight as a covariate, as well as a mixed-effects model for repeated measures (MMRM) in which between-group differences were considered significant if $p < .005$. Absolute and relative changes in blood pressure (postdose vs. predose) were assessed using descriptive statistics by visit and treatment. A formal pharmacokinetic analysis was not planned in this study, but accumulation was evaluated by calculating the ratios of bremelanotide concentrations on days 8 and 15 compared with day 2; accumulation was defined as a mean ratio with a 95% CI > 1 . Plasma for analysis was collected 1 h following the first dose on each of the 3 days. Safety was evaluated in all randomized subjects who received ≥ 1 dose of the study drug.

2.6.2 | Study B

Efficacy in Study B was evaluated in the intent-to-treat population, which included all randomized subjects who received ≥ 1 dose of the study drug and who had sufficient data for meaningful analysis. To be considered for analysis, data must be evaluable within the indicated timeframe or will be inspected on a case-by-case basis to determine if inclusion standards are met. A linear MMRM was used to evaluate differences in caloric intake between treatments, and an analysis of covariance model was used to evaluate differences in weight change from baseline between each treatment. For daily caloric intake, no correction for multiplicity was made. For both analyses, p -values

corresponding to two-sided tests were presented. Pharmacokinetic parameters were evaluated in the pharmacokinetic population, which included all subjects who had received bremlanotide and had sufficient concentration data to allow for calculation of the specified parameters. Pharmacokinetic parameters were calculated using WinNonlin® Professional version 5.2 (Pharsight Corp, Mountain View, CA, USA) by non-compartmental methods. Safety was evaluated in all randomized subjects who received ≥ 1 dose of the study drug. No adjustments were made to compensate for missing data.

3 | RESULTS

3.1 | Subjects

Demographic and clinical characteristics were similar between the two treatment groups in Study A (Table S1) and they were similar to

those in Study B, except that in Study A all subjects were white, whereas in Study B, 14 (51.9%) were white and 13 (48.1%) were black/African American. At baseline in Study A, the mean age was 34.3 for the placebo group and 34.7 years for the bremlanotide group. In Study B, the baseline mean age was 28.0 years for all groups. The mean baseline BMI was 33.6 for the placebo group and 33.5 kg/m² for the bremlanotide group in Study A. In Study B, it was 34.2 kg/m² for all groups. In Study A, the mean baseline waist circumference was 104.8 and 104.6 cm for the placebo and bremlanotide groups, respectively. The waist circumference was not reported in Study B.

3.1.1 | Study A

In Study A, 30 and 28 subjects received ≥ 1 dose of bremlanotide or placebo, respectively, and were included in the safety population. In

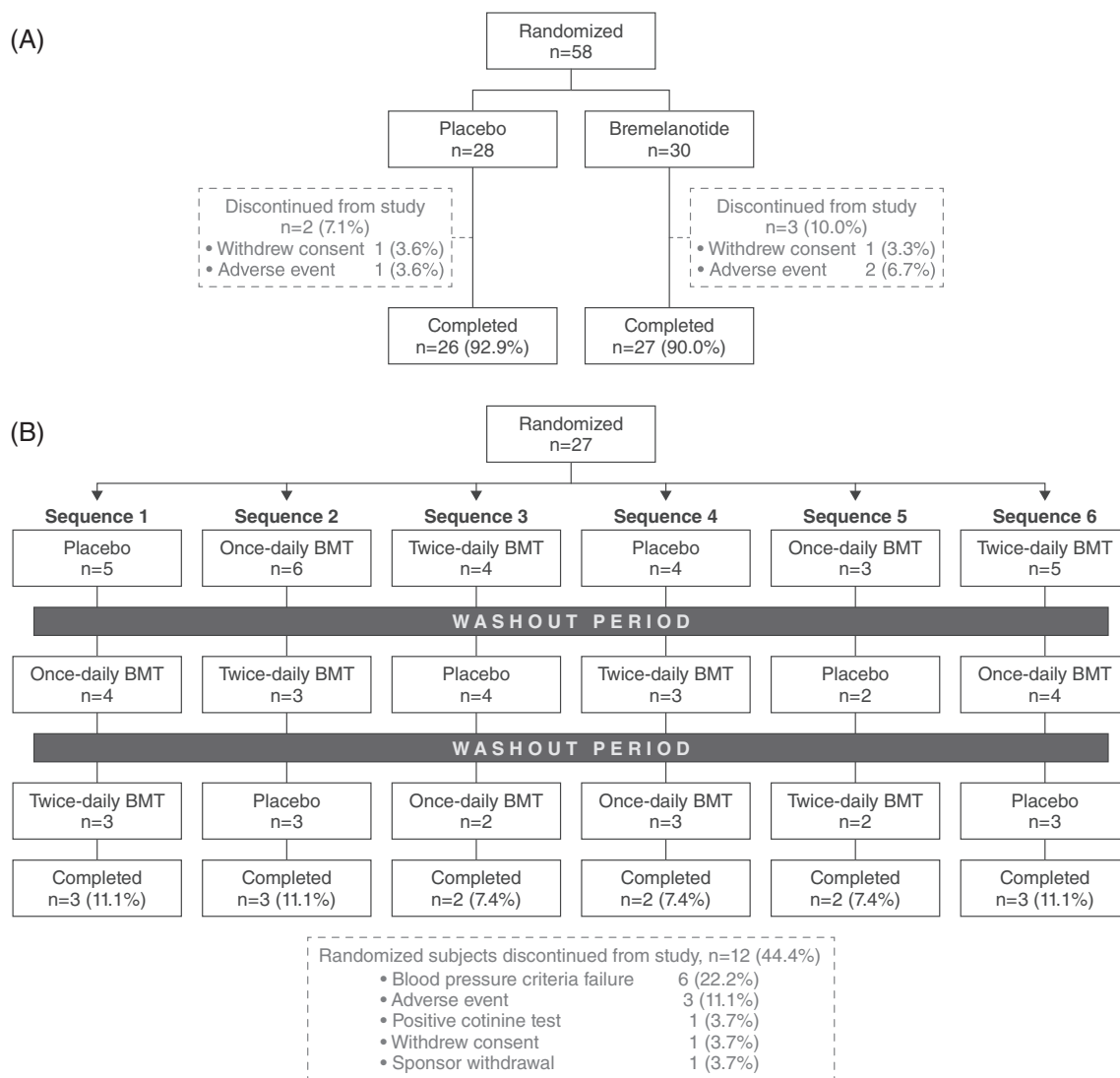


FIGURE 1 Disposition of subjects A) Study A. B) Study B. BMT, bremlanotide

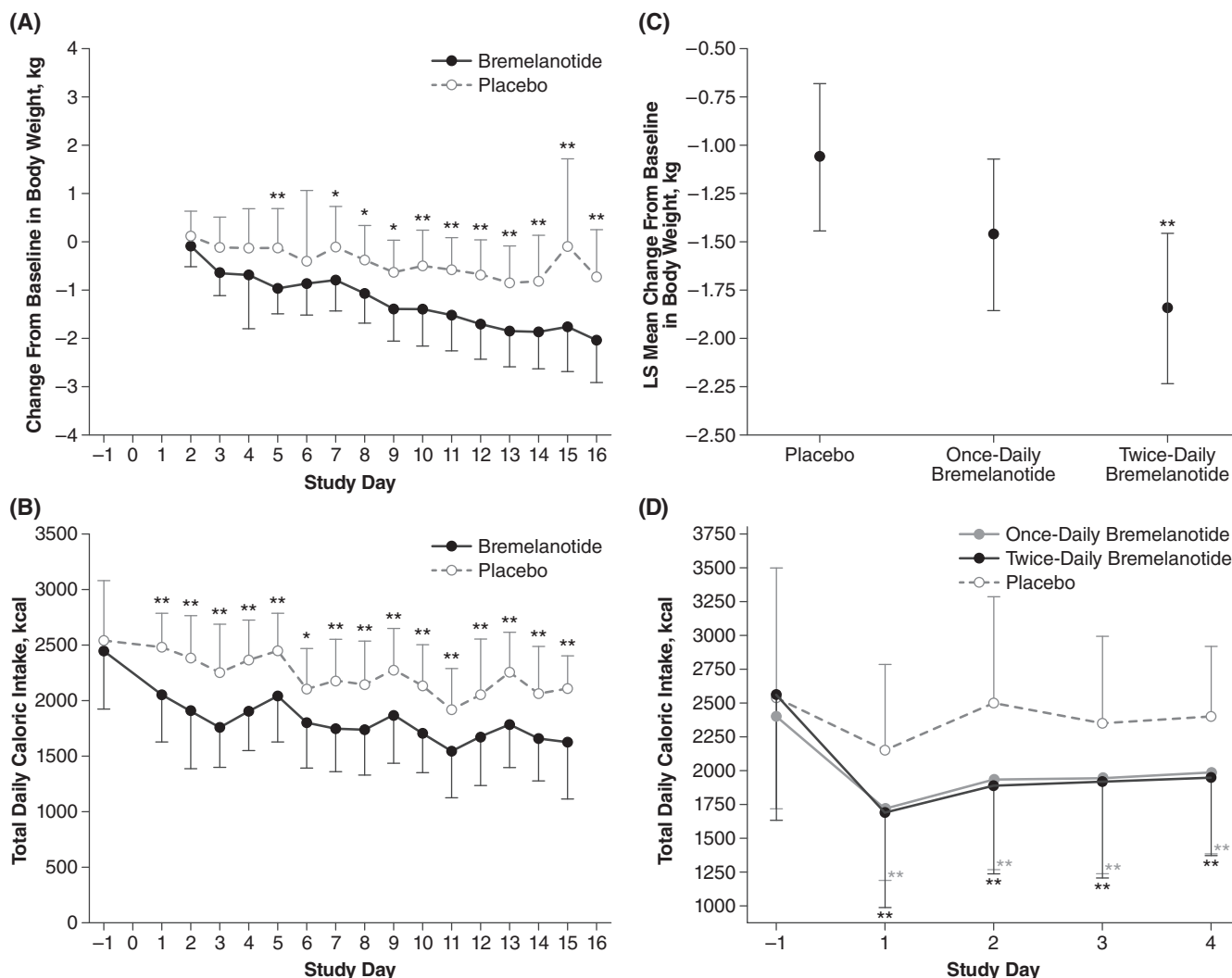


FIGURE 2 Changes from baseline in body weight and daily caloric intake for studies A and B A) Mean daily change from baseline in body weight, and B) Mean daily total caloric intake among subjects receiving bremelanotide or placebo 3 times daily for 15 days in Study A. C) LS mean change in body weight from baseline to day 4 among ITT subjects receiving once- or twice-daily bremelanotide or placebo in Study B. Analysis of covariance, * $P < 0.01$, ** $P < 0.001$. D) Mean daily total caloric intake over 4 days in each treatment group for ITT subjects in Study B. * $P < 0.01$, ** $P < 0.001$ (Study A: Mixed-effect repeated measures model. Study B: mixed-effect repeated measures model). ITT, intent to treat

the bremelanotide group, 27 of 30 subjects (90.0%) completed the study through day 16; three subjects withdrew because of AEs ($n = 2$) or withdrawn consent ($n = 1$). In the placebo group, 26 of 28 subjects (92.9%) completed the study; two subjects withdrew because of AEs ($n = 1$) or withdrawn consent ($n = 1$) (Figure 1A). Four of the five non-completers withdrew before day 8 and were therefore excluded from the per-protocol analysis population.

3.1.2 | Study B

Study B included 27 subjects, 15 of whom (55.6%) completed all three study phases. Demographic and clinical characteristics are provided in Table S1. In total, 12 subjects withdrew from the study. They withdrew because of blood pressure withdrawal criteria ($n = 6$), AEs

($n = 3$), withdrawn consent ($n = 1$), sponsor discretion ($n = 1$) and positive cotinine test results ($n = 1$) (Figure 1B). Of the six subjects that were discontinued because of blood pressure withdrawal criteria, four were receiving once-daily bremelanotide (2.5 mg/0 mg): two received bremelanotide and met criteria ~1 h after dosing on day 12 and 3 h after dosing on day 1, respectively, and the other two had just received placebo at the time of withdrawal. The remaining two subjects were receiving placebo (0 mg/0 mg) at the time of withdrawal. No subjects were withdrawn from the study while receiving the 2.5 mg/2.0 mg bremelanotide dosing regimen. No subjects had systolic or diastolic blood pressure readings above 155 mmHg or 95 mmHg, respectively. The intent-to-treat population included 20 subjects treated with twice-daily bremelanotide, 22 subjects treated with once-daily bremelanotide and 21 subjects given placebo.

3.2 | Weight and calorie intake

3.2.1 | Study A

After 16 days, subjects given placebo lost a least squares (LS) mean of 0.7 kg, compared with 2.1 kg among bremelanotide-treated subjects [LS mean difference (95% CI), -1.3 (-1.9 to -0.8) kg; $p < .0001$; Figure 2A]. Results of the MMRM revealed significant differences in weight loss between the two groups beginning on day 5 [LS mean difference (95% CI), -0.9 (-1.3 to -0.4); $p = .0003$] and continuing from day 7 to day 16 ($p < .01$). Mean daily caloric intake was similar between groups at baseline but was lower in the bremelanotide group versus the placebo group each day throughout the study (Figure 2B). Ranges of daily calories consumed were 1917-2478 kcal in the placebo group and 1541-2049 kcal in the bremelanotide group. Reductions in calorie consumption among subjects given bremelanotide versus placebo were similar in magnitude throughout the study (approximately 400 kcal/day, $p < .01$ on all treatment days) and were observed consistently at snacks and mealtimes except at breakfast, which needed to be eaten in full per protocol. The mean change in waist circumference from baseline to day 16 was minimal and no significant differences were observed in the bremelanotide-treated group compared with placebo (1.63% vs. 1.24% decrease in waist circumference, respectively).

3.2.2 | Study B

The mean weight loss from baseline after 4 days of treatment was significantly greater with twice-daily bremelanotide compared with placebo (1.7 vs. 0.9 kg, respectively, $p < .001$; Figure 2C). In the once-daily bremelanotide group, weight loss was numerically greater than weight loss observed in placebo-treated subjects, but the difference did not reach statistical significance ($p = .0805$). Daily caloric intake was significantly lower among subjects receiving bremelanotide versus those receiving placebo (either once or twice daily) on all four treatment days ($p < 0.001$; Figure 2D).

3.3 | Pharmacokinetics

3.3.1 | Study A

The mean ratios of day 8/day 2 and day 15/day 2 bremelanotide concentrations, respectively, were 1.0 (95% CI, 0.9-1.0) and 1.1 (95% CI, 1.0-1.2), indicating a lack of accumulation over the 15-day period.

3.3.2 | Study B

Pharmacokinetic analysis indicated rapid increases in bremelanotide concentration after SC administration, and similar concentration curves were observed following each dose in both bremelanotide treatment groups (Table 1). The day 4/day 1 ratio of plasma bremelanotide concentration 3.5 h postdose (accumulation ratio, $RACC_{3.5}$) was 1.0

TABLE 1 Pharmacokinetic parameters during once- and twice-daily bremelanotide dosing in Study B

Pharmacokinetic parameter, mean \pm SD	Once-daily bremelanotide (n = 17-22)	Twice-daily bremelanotide (n = 19-20)
AUC_{0-last} , ng-h/mL	277 \pm 51.5	475 \pm 75.2
$AUC_{0-3.5}$, ng-h/mL	181 \pm 35.4	176 \pm 32.6
C_{max} , ng/mL	75.1 \pm 16.1	83.8 \pm 15.6
C_{max} (D1), ng/mL	75.1 \pm 16.1	75.2 \pm 16.3
C_{avg} , ng/mL	25.2 \pm 4.7	41.7 \pm 9.3
C_{avg} (D1), ng/mL	51.6 \pm 10.1	50.2 \pm 9.4
t_{max} , h	1.0 \pm 0.3	3.3 \pm 2.0
t_{max} (D1), h	1.0 \pm 0.3	0.9 \pm 0.4
$RACC_{3.5}$ ^a	1.0 \pm 0.3	1.0 \pm 0.1

Abbreviations: $AUC_{0-3.5}$, area under the concentration versus time curve from dosing until 3.5 h postdose; AUC_{0-last} , area under the concentration versus time curve from dosing until the last time point; C_{avg} , average concentration over the full dosing interval; C_{max} , maximum observed concentration; D1, dose 1; t_{max} , time to maximum observed concentration; $RACC_{3.5}$, accumulation of bremelanotide at 3.5 h postdose.

^a $RACC_{3.5}$ was calculated as the ratio of day 4/day 1 bremelanotide concentrations observed 3.5 h postdose.

with both once- and twice-daily dosing, indicating no evidence of accumulation over 4 days.

3.4 | Safety

3.4.1 | Study A

Transient changes in blood pressure observed 1 h following each injection were minimal and relatively consistent across the placebo and bremelanotide groups (Table S2). Over the course of the study, subjects in both the placebo and bremelanotide groups showed a slight decrease from baseline ($<10\%$) in mean systolic and diastolic blood pressure.

All 58 subjects, including those in the placebo group, experienced ≥ 1 AE judged by the investigator as potentially related to treatment (Table 2). Injection site reactions were the most frequently observed treatment-related AEs (experienced by $>96\%$ of subjects in both groups), and no SAEs were reported during the study. Skin hyperpigmentation and nausea were more commonly reported among subjects receiving bremelanotide versus placebo. Three subjects withdrew from the study owing to AEs, including one subject in the placebo group following an event of vomiting and two subjects in the bremelanotide group following events of hypertension and nausea ($n = 1$ each). Changes in libido were not monitored or reported in Study A.

3.4.2 | Study B

All 27 subjects experienced ≥ 1 AE judged potentially related to treatment at some point throughout the study, including 20 of 21 subjects

TABLE 2 Adverse events experienced in each treatment group in Study A

	Placebo (n = 28)	Bremelanotide (n = 30)
Subjects experiencing ≥ 1 AE, n (%)	28 (100)	30 (100)
Mild	26 (92.9)	21 (70.0)
Moderate	2 (7.1)	9 (30.0)
Severe	0	0
Subjects experiencing each AE type, ^a n (%)		
Injection site reaction	27 (96.4)	30 (100)
Skin hyperpigmentation	2 (7.1)	19 (63.3)
Headache	10 (35.7)	12 (40.0)
Nausea	4 (14.3)	9 (30.0)
Decreased appetite	2 (7.1)	7 (23.3)
Ecchymosis	11 (39.3)	5 (16.7)
Contact dermatitis	0	4 (13.3)
Flushing	0	4 (13.3)
Dizziness	3 (10.7)	3 (10.0)
Somnolence	2 (7.1)	3 (10.0)
Petechiae	1 (3.6)	3 (10.0)
Abdominal discomfort	0	3 (10.0)
Constipation	4 (14.3)	2 (6.7)
Nasal congestion	2 (7.1)	2 (6.7)
Abdominal pain	1 (3.6)	2 (6.7)
Feeling hot	0	2 (6.7)
Musculoskeletal pain	0	2 (6.7)
Myalgia	0	2 (6.7)
Abnormal urine odour	0	2 (6.7)
Hyperesthesia	0	2 (6.7)
Subjects experiencing ≥ 1 treatment-related AE, n (%)	28 (100)	30 (100)
Subjects experiencing each treatment-related AE type, ^a n (%)		
Injection site reaction	27 (96.4)	30 (100)
Skin hyperpigmentation	2 (7.1)	19 (63.3)
Headache	7 (25.0)	10 (33.3)
Nausea	3 (10.7)	9 (30.0)
Decreased appetite	2 (7.1)	7 (23.3)
Flushing	0	4 (13.3)
Somnolence	2 (7.1)	3 (10.0)
Ecchymosis	5 (17.9)	2 (6.7)
Hyperesthesia	0	2 (6.7)
Dizziness	1 (3.6)	2 (6.7)
Feeling hot	0	2 (6.7)
Abdominal discomfort	0	2 (6.7)
Subjects experiencing ≥ 1 SAE	0	0
Subjects experiencing an AE leading to treatment discontinuation, n (%)	1 (3.6)	2 (6.7)
Hypertension	0	1 (3.3)
Nausea	0	1 (3.3)
Vomiting	1 (3.6)	0

Abbreviations: AE, adverse event; SAE, serious adverse event.

^aList includes all AEs or treatment-related AEs experienced by ≥ 2 subjects in the bremelanotide group.

TABLE 3 Adverse events experienced during each treatment phase in Study B

	Placebo (n = 21)	Once-daily bremelanotide (n = 22)	Twice-daily bremelanotide (n = 20)
Subjects experiencing ≥ 1 AE, n (%)	20 (95.2)	21 (95.5)	20 (100)
Mild	20 (95.2)	21 (95.5)	20 (100)
Moderate	2 (9.5)	4 (18.2)	1 (5.0)
Severe	0	0	0
Subjects experiencing each AE type, ^a n (%)			
Injection site reaction	12 (57.1)	16 (72.7)	20 (100)
Injection site pain	17 (81.0)	7 (31.8)	8 (40.0)
Injection site erythema	5 (23.8)	9 (40.9)	5 (25.0)
Nausea	1 (4.8)	4 (18.2)	4 (20.0)
Headache	0	2 (9.1)	4 (20.0)
Flushing	0	4 (18.2)	3 (15.0)
Injection site pruritus	1 (4.8)	2 (9.1)	3 (15.0)
Flatulence	0	1 (4.5)	3 (15.0)
Skin hyperpigmentation	1 (4.8)	0	3 (15.0)
Pigmentation disorder	0	6 (27.3)	2 (10.0)
Libido increased	0	3 (13.6)	2 (10.0)
Injection site swelling	2 (9.5)	2 (9.1)	2 (10.0)
Ephelides	3 (14.3)	0	2 (10.0)
Vessel puncture site haemorrhage	0	0	2 (10.0)
Decreased appetite	1 (4.8)	2 (9.1)	0
Procedural dizziness	0	2 (9.1)	0
Feeling hot	0	2 (9.1)	0
Subjects experiencing ≥ 1 treatment-related AE, n (%)	20 (95.2)	21 (95.5)	20 (100)
Subjects experiencing each treatment-related AE type, ^a n (%)			
Injection site reaction	12 (57.1)	16 (72.7)	20 (100.0)
Injection site pain	17 (81.0)	7 (31.8)	8 (40.0)
Injection site erythema	5 (23.8)	9 (40.9)	5 (25.0)
Nausea	1 (4.8)	4 (18.2)	3 (15.0)
Flushing	0	4 (18.2)	3 (15.0)
Injection site pruritus	1 (4.8)	2 (9.1)	3 (15.0)
Headache	0	2 (9.1)	3 (15.0)
Skin hyperpigmentation	1 (4.8)	0	3 (15.0)
Pigmentation disorder	0	6 (27.3)	2 (10.0)
Libido increased	0	3 (13.6)	2 (10.0)
Injection site swelling	2 (9.5)	2 (9.1)	2 (10.0)
Flatulence	0	1 (4.5)	2 (10.0)
Ephelides	3 (14.3)	0	2 (10.0)
Decreased appetite	1 (4.8)	2 (9.1)	0
Feeling hot	0	2 (9.1)	0
Subjects experiencing ≥ 1 SAE	0	1 (4.5) ^b	0
Subjects experiencing an AE leading to treatment discontinuation, n (%)	0	2 (9.1)	1 (5.0)
Nausea	0	1 (4.5)	0
Vomiting	0	1 (4.5)	1 (5.0)

Abbreviations: AE, adverse event; SAE, serious adverse event.

^aList includes all AEs or treatment-related AEs experienced by ≥ 2 subjects in either of the bremelanotide groups.

^bOne subject experienced five SAEs during once-daily bremelanotide treatment: mild nausea, mild vomiting, mild headache, moderate hypersensitivity (all classified as potentially related to treatment), and moderate dizziness classified as unrelated to treatment.

(95.2%) during placebo administration, 21 of 22 subjects (95.5%) during once-daily bremelanotide treatment, and 20 of 20 subjects (100%) during twice-daily bremelanotide treatment (Table 3). These events were primarily injection site reactions of mild or moderate severity. Skin hyperpigmentation, nausea, headache and flushing occurred more frequently during bremelanotide versus placebo administration. Five SAEs were reported in a single subject while receiving once-daily bremelanotide (nausea, vomiting, hypersensitivity, dizziness, headache), four of which were deemed possibly, probably, or definitely related to study treatment (dizziness was judged as unlikely to be treatment related). The subject withdrew following these events. Two additional subjects withdrew following an event of mild vomiting during twice-daily bremelanotide treatment and an event of moderate nausea during once-daily bremelanotide treatment. Increased libido was reported by three subjects (13.6%) while receiving the 2.5 mg/0 mg treatment, and two subjects (10.0%) while receiving the 2.5 mg/2.0 mg treatment. All of these AEs were considered mild in severity.

4 | DISCUSSION

In Studies A and B, caloric intake was immediately reduced within 1 day of bremelanotide treatment, and significant weight loss was observed within 1 week. In Study B, significant weight loss (mean of 1.7 kg per subject) was observed after only 4 days of twice-daily treatment. Bremelanotide was generally well tolerated in both studies. In Study B, rapid absorption of bremelanotide was observed after SC administration, and data from both studies indicated a lack of accumulation after 4 or 15 days of treatment.

The evaluation of blood pressure was an objective of Study A, and no clinically meaningful differences in either transient or persistent blood pressure fluctuations were observed between the placebo and bremelanotide groups. Differences in blood pressure between the two groups were present at baseline and consistent throughout the 16-day study. Study B exhibited a higher withdrawal rate of subjects failing to meet blood pressure criteria than Study A. However, of the six subjects that were discontinued because of blood pressure withdrawal criteria, only two had received bremelanotide and met criteria ~1 h after dosing on day 12 and 3 h after dosing on day 1, respectively. The others had just received the placebo dose in the bremelanotide/placebo regimen, or were on twice-daily placebo at the time of withdrawal. Changes in blood pressure were not a primary objective in Study B and the withdrawal criteria helped to minimize risk in the study population. These results were in line with data collected during the clinical development of bremelanotide for hypoactive sexual desire disorder, which showed that blood pressure levels following bremelanotide treatment were not related to drug exposure and that treatment was not associated with persistent hypertension.⁹ Despite the lack of a significant association, elevated blood pressure is a safety concern that should be continually monitored in adults

using MC4R agonists such as bremelanotide. Nausea was a relatively common treatment-related AE among subjects receiving bremelanotide in both Study A and Study B (experienced by ~18% to 30% of subjects receiving bremelanotide across studies), but only one subject in each study discontinued owing to nausea. Prospective patients need to take this elevated nausea risk into account before and during bremelanotide treatment, particularly if they are already prone to severe nausea. Upon conferral with their respective physician, patients can make an informed decision on whether or not starting an MC4R agonist such as bremelanotide is in their best interest.

These prospective clinical studies had several strengths, including the robustness of the randomized, double-blind, placebo-controlled designs. Study B also employed a crossover design to minimize between-group effects owing to differences in subject characteristics. A major limitation of both studies was the relatively short treatment duration, as well as the lack of data collected after the end of treatment. Both studies also had a small number of subjects. Future studies with larger study populations, longer treatment durations, and patient follow-up are required to verify these data and to determine the effect of treatment cessation.

The clinical study results presented here suggest that bremelanotide may reduce caloric intake and promote weight loss among women with obesity. Effects on appetite may be observed immediately, and substantial weight loss may occur within 1 week of initiating treatment. Together, these data provide evidence that agonism at the MC4R receptor promotes appetite suppression and resulting weight loss among women with obesity, laying the foundation for future studies and therapeutic advances.

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CONFLICT OF INTEREST

Robert Jordan and Carl Spana are employees of Palatin Technologies, Inc. Steven Fischkoff was an employee of Palatin Technologies, Inc. at the time that the work was conducted.

DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/dom.14672>.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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