ORIGINAL RESEARCH—WOMEN'S SEXUAL HEALTH

An Effect on the Subjective Sexual Response in Premenopausal Women with Sexual Arousal Disorder by Bremelanotide (PT-141), a Melanocortin Receptor Agonist

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ABSTRACT

Introduction. Melanocortins affect multiple physiological responses, including sexual behaviors. Bremelanotide is a synthetic peptide melanocortin analog of α-melanocyte-stimulating hormone that is an agonist at melanocortin receptors MC3R and MC4R.

Aim. To evaluate a single intranasal dose of bremelanotide for potential effects on physiological and subjective measurements of sexual arousal and desire in premenopausal women with sexual arousal disorder.

Main Outcome Measures. Change in vaginal pulse amplitude during neutral and erotic videos after treatment with bremelanotide or placebo and subjects' perceptions of physiological and sexual response within 24 hours of treatment with bremelanotide or placebo.

Methods. Eighteen premenopausal women with a primary diagnosis of female sexual arousal disorder were randomly assigned to receive a single intranasal dose of 20 mg bremelanotide or matching placebo in a double-blind manner during the first in-clinic treatment session, and the alternate medication during the second in-clinic treatment session. During each session, subjects viewed a 20-minute neutral video followed by a 20-minute sexually explicit video. Vaginal photoplethysmography was used to monitor vaginal vasocongestion and questionnaires were used to evaluate perceptions of sexual response within the following 24-hour period.

Results. More women reported moderate or high sexual desire following bremelanotide treatment vs. placebo ($P = 0.0114$), and a trend toward more positive responses regarding feelings of genital arousal occurred after bremelanotide compared with placebo ($P = 0.0833$). Among women who attempted sexual intercourse within 24 hours after treatment, significantly more were satisfied with their level of sexual arousal following bremelanotide, compared with placebo ($P = 0.0256$). Vaginal vasocongestion did not change significantly while viewing erotic videos following bremelanotide administration compared with placebo.

Conclusion. This preliminary evaluation suggests the potential for bremelanotide to positively affect desire and arousal in women with female sexual arousal disorder and indicates that bremelanotide is a promising candidate for further evaluation in an at-home study. **Diamond LE, Earle DC, Heiman JR, Rosen RC, Perelman MA, and Harning R. An effect on the subjective sexual response in premenopausal women with sexual arousal disorder by bremelanotide (PT-141), a melanocortin receptor agonist. J Sex Med 2006;3:628–638.**

Key Words. Neurophysiological Studies of Sexual Function; Pharmacological Studies in Sexual Function; Central Nervous System Control

Introduction

While the understanding of the pathophysiology of male erectile dysfunction has progressed rapidly in the past decade and has led to several new therapeutic modalities, much less has been done to address similar issues in women's sexual health, despite evidence suggesting that the prevalence of female sexual dysfunction (FSD) may surpass that of sexual dysfunction in men [1–5].

The investigation of FSD is complex. Psychosocial, relational, physiological, and pharmacological variables interact individually in each woman to produce an array of sexual outcomes. Sexual dysfunctions in women have been categorized into specific disorders: desire disorder, arousal disorder, orgasmic disorder, and sexual pain disorders. These classifications are heuristic conveniences for providing working definitions and an accepted lexicon for researchers and therapists. While these dysfunctions can occur independently of each other, they frequently cluster together [6]. In some instances, it might be possible to identify a primary disorder, but often this is not the case. The current definitions of FSD disorders imply an independence of etiology and primacy [7].

Female sexual arousal disorder (FSAD), one of the female sexual disorder categories, was originally defined by a working group of the American Foundation for Urologic Disease as: "The persistent or recurrent inability to attain or maintain sufficient sexual excitement, causing personal distress. It may be expressed as a lack of subjective excitement or a lack of genital (lubrication/swelling) or other somatic responses" [8]. Newly revised definitions differentiate between subjective, genital, and combined genital and subjective sexual arousal disorder [7].

Cardiovascular risk factors have been shown to correlate with complaints of vaginal and clitoral dysfunction in some women [9–12], although one recently completed study did not find a correlation between FSD and self-reported vascular disease [13]. It has consequently been hypothesized that FSAD may be amenable to treatment with vasodilators or pharmacological agents that modulate the autonomic nervous system [14–19]. Several clinical trials have evaluated the efficacy of sildenafil, a type 5 phosphodiesterase inhibitor, which is a potent vasodilator and a highly successful medication for erectile dysfunction, with largely negative results for FSD [20–23].

Bremelanotide, a synthetic peptide melanocortin analog of α-melanocyte-stimulating hormone (α-MSH) that is an agonist at melanocortin receptors MC3R and MC4R, is currently in development for the treatment of erectile dysfunction. It has been shown in animal models that melanocortins affect multiple physiological responses via a central mechanism, including sexual behaviors [24]. Effects of α-MSH on sexual behaviors, such as yawning, grooming, stretching, and penile erections, have been observed in laboratory animals and it is believed to act downstream from dopamine and oxytocin in hypothalamic centers adjacent to the third ventricle [25–27]. A central mechanism of action for bremelanotide is inferred by the localization of its target receptors in the hypothalamus and by results of animal studies showing enhanced expression of c-fos in regions of the brain associated with sexual responses after peripheral administration of bremelanotide [28,29]. Studies in normal healthy male volunteers provide further support for the hypothesis that bremelanotide is a central initiator of erectile activity in men [30,31].

While there are gender differences in the patterning of psychophysiological reactions to sexual stimulation and it is well established that most women complaining of chronic low arousal show vasocongestive responses to erotic stimuli that are comparable to controls [32–35], the evidence indicating a central mechanism of action for bremelanotide supports exploratory inquiry on the potential for this agent to affect sexual arousal in women. A preclinical study that examined the dose–response effects of bremelanotide on proceptive sexual behaviors, such as solicitation, hops and darts, and pacing, and receptive sexual behaviors, such as lordosis, in ovariectomized female rats, demonstrated a clear-cut pharmacological initiation of appetitive sexual behaviors in female rats primed with estrogen and progesterone or with estrogen alone [36]. While it is unclear what might be the human analog to appetitive behavior in female rats, it may be speculated that sexual interest, desire, and perhaps arousal are associated with these behaviors, indicating a potential role for bremelanotide as a pharmacological intervention for FSD.

Based on the erectogenic properties of bremelanotide via a unique mechanism of action, and encouraging results in female animal studies, this exploratory in-clinic study was performed to examine the potential effects of bremelanotide on the physiological and/or subjective sexual response when administered to premenopausal women with a primary complaint of FSAD. Given the high

frequency of discordance among various response measures, this was designed primarily as a proof-of-concept study to discern which, if any, quantitative or subjective measures might detect a drug effect.

Aims

To evaluate a single intranasal dose of bremelanotide for potential effects on physiological and subjective measurements of sexual arousal, and subjective measures of desire in premenopausal women with FSAD. To evaluate significant covariates or predictors of increased sexual response in conjunction with a single dose of bremelanotide in premenopausal women with FSAD.

Methods

Study Population

Eighteen premenopausal women between the ages of 22 and 44 years with a primary diagnosis of FSAD were enrolled into this randomized, double-blind, placebo-controlled crossover pilot study. The diagnosis of FSAD was established upon examination by an expert sexual health clinician (M.A.P.), a score of <3 for the arousal domain of the Female Sexual Function Index (FSFI) [37], and a score of above 40 on the Female Sexual Distress Scale [38]. Subjects were required to have a previous history of a normal and satisfying sexual response. No attempt was made to differentiate FSAD due primarily to lack of subjective excitement or lack of genital response. During the diagnostic examination for FSAD, subjects often reported both a mental and physical reduction in arousal from some earlier point in life; and as predicted by the sexual tipping point™ model, this usually reflected an alteration in both psychosocial and physiological factors [39]. A woman's subjective experience of arousal was usually influenced by genital feedback, and frequently the women would describe "feeling less." For many subjects, this alteration in arousal presented with a secondary and/or associated diminishment in desire, although the comorbid nature of these variables was often difficult to tease apart.

Subjects were excluded from study participation if they met any of the following criteria: pregnant or nursing; uncontrolled diabetes mellitus or hypertension; history or evidence of unresolved sexual trauma or abuse; primary anorgasmia, vaginismus, sexual pain disorder, or sexual aversion disorder; genitorurinary infections or inflammation; history of diagnosed psychosis or manic depression within the past year; use of antidepressants, antipsychotics, or any product indicated for the treatment of sexual dysfunction. Subjects of child-bearing potential were required to use an approved method of birth control.

Study Design and Procedures

Following a screening visit that included a physical examination, a 12-lead resting electrocardiogram (ECG), and clinical laboratory tests (chemistry, hematology, serum pregnancy, urinalysis, and endocrinology), eligible subjects were randomly assigned to receive a single intranasal dose of 20 mg bremelanotide or matching placebo during the first treatment session, and the alternate medication during the second treatment session. Visits were scheduled to exclude times during which subjects were menstruating, but no other timing relative to menstrual cycles was attempted. During each treatment session, scheduled 2–7 days apart, subjects viewed a 20-minute neutral video, which began 5 minutes after administration of study drug, followed 10 minutes later by a 20-minute sexually explicit video depicting nude, heterosexual couples engaging in consensual foreplay and intercourse. All subjects viewed the same set of videos (two neutral, two sexually explicit) in a random order in a private room at a clinical research center.

Vaginal pulse amplitude (VPA) was monitored continuously from 20 minutes prior to dosing until 60 minutes after dosing. Data were recorded at a sampling rate of 200 samples/second on an HP Personal Computer using the software program AcqKnowledge III, Version 3.7.3 (BIOPAC Systems, Inc., Santa Barbara, CA, USA) and a Model MP150WSW data acquisition unit (BIOPAC Systems, Inc.) for analog/digital conversion. The signal was band-pass filtered (0.5–30 Hz). The vaginal probe (Behavioral Technology Inc., Salt Lake City, UT, USA) was inserted into the subject's vagina by the investigator to ensure consistency in probe placement, and the incoming signal was calibrated before each session using the zero adjustment knob on the MP150WSW unit. The depth of the probe and orientation of the light-emitting diode were standardized at the time of each probe placement. VPA data were hand-scored by an independent consultant who was blinded to the treatment schedule. For each experimental condition, the maximum peak-to-peak amplitude that was sustained for a minimum of 60 seconds was measured in millimeters at baseline (T-20–T0), and during the neutral (T5–T25) and erotic (T35–T55) films.

Prior to initiation of each in-clinic treatment session, the investigator reviewed the sequence of events with each subject, subjects were asked to remain as still as possible after the vaginal probe was inserted, and reminded to complete and return by mail the questionnaire that assessed the subject's experience during the 24-hour post-dose period. No instructions were provided to subjects regarding whether direct genital stimulation was allowed during the video sessions, and no instructions were provided to subjects regarding whether sexual relations should be attempted after the in-clinic treatment period. No study personnel were in the room with the subject for the duration of the video series.

Immediately before and after each film presentation, subjects completed a 39-item self-report questionnaire that assessed sexual arousal, perceptions of physical change, autonomic arousal, and positive and negative reactions to each film [40]. A Treatment Satisfaction Questionnaire (developed by J.R.H. and A. Friedman specifically for this study) was given to each subject to complete 24 hours following study drug administration. This questionnaire assessed subjective levels of arousal and desire during the 24-hour post-dose period, as well as sexual activity that might have occurred during this time period.

Sitting blood pressure and pulse rate were measured prior to dosing and 1 and 3 hours after dosing. A 12-lead resting ECG, physical examination, blood pressure and pulse rate assessment, and laboratory tests (hematology and chemistry) were performed prior to discharge from the study at the second treatment visit. Adverse events were assessed throughout the treatment session and via a telephone call placed 24 hours after each study drug administration.

Following completion of the clinical study, unblinded, exploratory, in-depth individual interviews were conducted on a voluntary basis by an independent professional moderator to obtain qualitative responses from each subject regarding their subjective experience during and after each treatment session. Because this was an exploratory, hypothesis-generating study, rather than a study intended to confirm one or more hypotheses, the use of unblinded, open-ended, qualitative interviews was deemed to be an effective and justifiable method to illuminate potential variables and relationships that may be more fully and carefully explored in future studies [41].

A centralized institutional review board approved the study protocol and informed consent document prior to the enrollment of research subjects. All volunteers gave written informed consent prior to their participation in the study. The study was conducted in compliance with a written protocol and applicable Food and Drug Administration regulations and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines to insure adherence to good clinical practice standards and regulatory requirements.

Data Analysis

For the primary physiological variable of VPA, a measurement representing the maximum amplitude of response during the 20-minute period of neutral video was compared with a comparable measure of response (maximum VPA) during the 20-minute period of erotic video presentation, measured separately for each treatment, yielding a variable termed "maximum amplitude change." Comparisons of this calculated variable for bremelanotide effects compared with placebo administration were performed using the paired *t*-test. A similar comparison was made for the maximum VPA measured during the baseline period, prior to administration of study drug. Subjective assessments of responses to videos were analyzed using the Wilcoxon rank-sum test. Responses to the Treatment Satisfaction Questionnaire were analyzed for a treatment effect using McNemar's test for questions 1–5 and Fisher's exact test for questions 6–14.

Main Outcome Measurements

The main outcome measures were changes in VPA during neutral and erotic videos after administration of placebo and bremelanotide, and comparison of answers to questionnaires that assessed each subject's perception of her physiological and sexual response within the 24 hours following each treatment. As an exploratory post hoc analysis, an independent rater summarized trends observed based on unblinded in-depth individual interviews conducted with a subset of subjects after discharge from the study by an independent professional moderator.

Results

Demographics

Eighteen women were enrolled and completed the study. Table 1 shows baseline demographic char-

Table 1 Baseline demographic characteristics

Characteristic	Value
Age (years)	
Mean (SD)	34.2 (8.0)
Range	22–44
Weight (kg)	
Mean (SD)	71.8 (10.1)
Range	58.6–91.3
Height (cm)	
Mean (SD)	163.4 (6.7)
Range	149.9–177.8
Body mass index (kg/m^2)	
Mean (SD)	27.0 (4.2)
Range	19.8–35.2
Race, N (%)	
African American	8 (44.4%)
Caucasian	6 (33.3%)
Latino/Hispanic	4 (22.2%)
FSFI scores: mean (SD); range	
Desire	2.13 (1.05); 1.2–4.8
Arousal	1.93 (0.51); 1.2–2.7
Lubrication	2.62 (1.14); 0.6–5.1
Orgasm	1.95 (0.94); 1.2–4.0
Satisfaction	2.21 (0.69); 1.2–3.6
Pain	5.11 (1.25); 2.4–6.0
Female Sexual Distress Scale score	
Mean (SD)	50.5 (1.36)
Range	40–60
Total testosterone (ng/dL)*	
Mean (SD)	40.72 (19.44)
Range	12–95
Sex hormone-binding globulin (nm/L)†	
Mean (SD)	65.97 (51.77)
Range	12.1–180
Method of birth control, N (%)	
Hormonal contraceptives	15 (83.3%)
Bilateral tubal ligation	3 (16.7%)

*Normal range: 6–82 ng/dL (analyzed by radioimmunoassay, Bio-Reference Laboratories, Elmwood Park, NJ, USA). Mean (SD) total testosterone for subjects <34 years: 50.63 (20.02) ng/dL; for subjects ≥34 years: 32.8 (15.66) ng/dL.
†Normal range: 18–114 nm/L (Bio-Reference Laboratories, Elmwood Park, NJ, USA). Mean (SD) sex hormone-binding globulin for subjects <34 years: 75.13 (65.24) nm/L; for subjects ≥34 years: 58.65 (40.23) nm/L.

acteristics of the study population. Subsequent to questionnaire screening, all women were individually interviewed by an expert sexual health clinician (M.A.P.) to confirm a primary complaint of FSAD and suitability for study participation.

Laboratory Assessment

The maximum amplitude change in VPA during each laboratory assessment visit was expressed as maximum VPA during the erotic video presentation relative to maximum VPA during the neutral video. The value for each individual at each treatment session (N = 18) was calculated by dividing the difference between the maximum VPA during the neutral video phase (NV) and the maximum VPA during the erotic video (EV) by the maximum VPA during the neutral video, and multiplying by 100% (+[EV – NV]/NV * 100%). Based on this ratio score, the mean (±SD) maximum amplitude change in VPA measured after placebo treatment was 14.9% (17.1), and the mean (±SD) maximum amplitude change in VPA measured after bremelanotide treatment was 9.6% (13.3). The difference between these two values was not statistically significant ($P = 0.27$). Marked variability among individuals was noted, however, with percent changes in VPA ranging from –11.0% to 49.0% after the placebo treatment, and from 13.0% to 35.1% following bremelanotide treatment.

Vaginal pulse amplitude measurements during neutral and erotic videos were compared separately to baseline (BL) VPA [(+[NV – BL]/BL * 100%) and (+[EV – BL]/BL * 100%), respectively] to derive maximum amplitude changes in VPA relative to baseline for each individual. The mean (SD) of these two derived values after placebo vs. bremelanotide treatment was not significantly different (placebo: 14.81% [16.99]; bremelanotide: 9.17% [14.48]; $P = 0.23$).

A comparison of responses to the 39-item self-report questionnaire that was administered prior to and immediately following each video demonstrated no significant differences between the bremelanotide and placebo treatment groups. However, pooled analyses of responses following the neutral vs. erotic video revealed that subjects did report significantly ($P < 0.05$) increased feelings of sexual arousal following the erotic vs. neutral video (data not shown).

At-Home Experience: 24 Hours After Dosing

In order to assess, in an exploratory design, the experience of each subject during the 24 hours following dosing, subjects were asked to complete a Treatment Satisfaction Questionnaire (Table 2) after each treatment visit. Importantly, subjects were not instructed in any way as to what would or should transpire during this 24-hour period.

There was not a significant difference in responses based on treatment to the questions: "How often did you think about sex?" and "Did you have sexual fantasies?" However, positive responses occurred significantly more often to the question "Did you experience any sexual desire?" following bremelanotide administration, compared with placebo ($P = 0.0114$). While not reaching statistical significance, a higher number of positive responses were given following bremelanotide treatment compared with placebo for the question "Did you have any feelings of genital arousal?" ($P = 0.0833$). As shown in Figure 1, 72% of the women reported feelings of genital arousal

Table 2 Treatment Satisfaction Questionnaire responses

P value*	#	Question	Criteria for evaluation of response	
			Negative	Positive
0.3173	1	How often did you think about sex?	0–2 times†	3–6 times†
0.0833	2	Did you have any feelings of genital arousal?	No	Yes
0.7055	3	Did you have any sexual fantasies?	No	Yes
0.0114	4	Did you experience any sexual desire?	No/slight†	Moderate/high†
0.7630	5	Did you have any sexual activity?	No	Yes
0.1189	6	Did you initiate this activity?	No	Yes
0.0769	7	How would you rate your level of desire during this sexual encounter?	No/slight†	Moderate/high†
0.4667	8	Did you experience any lubrication?	No/slight†	Moderate/heavy†
0.0769	9	How would you rate your level of sexual arousal?	No/slight†	Moderate/high
0.1189	10	How difficult was it for you to become aroused?	No/slight†	Moderate/very†
0.0256	11	Were you satisfied with your level of arousal?	No/slight†	Moderate/very†
1.0000	12	Did you achieve orgasm?	No	Yes
0.5227	13	How difficult was it for you to achieve orgasm?	No/slight†	Moderate/very†
1.0000	14	Were you satisfied with the level of intensity of your orgasm?	No/slight†	Moderate/very†

*Responses to questions 1–5 were evaluated using McNemar's test and responses to questions 6–14 were evaluated using Fisher's exact test.
†A total of four possible responses were combined into two categories for analysis.
Questionnaires were given to subjects after each treatment visit with instructions to complete and return the questionnaire to the clinical site within 24 hours using the self-addressed stamped envelope provided. All subjects were instructed to complete questions 1–5. A positive response to question 5 required completion of questions 6–12, and a positive response to question 12 required completion of questions 13 and 14.

following bremelanotide treatment, compared with a 39% response rate after placebo treatment, and 67% and 22% of the women reported experiencing sexual desire after bremelanotide and placebo treatment, respectively. The association between a positive response rate to the question regarding arousal with a positive response rate to the question regarding desire was statistically stronger in the bremelanotide treatment group compared with the placebo treatment group (Fisher's exact test, $P < 0.0001$). No sequence effect on responses to the Treatment Satisfaction Questionnaire was noted.

Thus, 12 of 18 subjects (67%) recorded a positive response to questions regarding both arousal and desire following bremelanotide treatment, while 4 of 18 (22%) subjects responded accordingly after placebo treatment. Eight and seven women engaged in sexual activity following bremelanotide and placebo treatment, respectively. Analysis of questionnaire responses (Table 2) demonstrated that significantly more women were satisfied with their level of sexual arousal during the sexual experience following bremelanotide treatment compared with placebo treatment ($P = 0.0256$). While the difference did not reach significance, subjects assigned a higher rating to their desire and arousal during the sexual experience following bremelanotide vs. placebo treatment ($P = 0.0769$ for both assessments).

Age as a Covariate for Response

A retrospective analysis of the influence of age on responses to the Treatment Satisfaction Questionnaire following each treatment visit was performed by comparing the subgroups of women less than 34 years of age (N = 8) with those 34 years of age

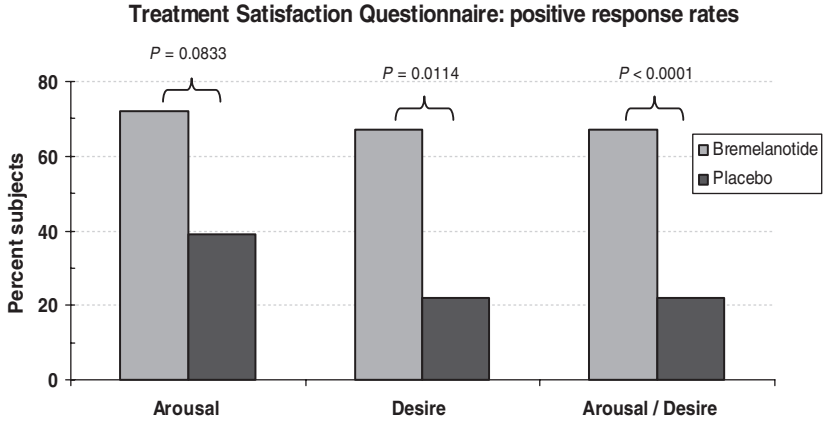

Figure 1 Positive response rates of subjects after treatment with bremelanotide and after treatment with placebo to Treatment Satisfaction Questionnaire questions: "Did you have any feelings of genital arousal?" and "Did you experience any sexual desire?," and response rate of subjects who reported a positive response to both questions.

Table 3 Treatment Satisfaction Questionnaire responses by age

P value*			
Age < 34	Age ≥ 34	#	Question
0.5637	0.4142	1	How often did you think about sex?
1.000	0.0339	2	Did you have any feelings of genital arousal?
0.5637	1.000	3	Did you have any sexual fantasies?
0.5637	0.0082	4	Did you experience any sexual desire?

*Responses to questions 1–5 were evaluated using McNemar's test. Criteria for response evaluation were the same as for Table 2.

or older (N = 10). This subgrouping was derived using the mean age (34.2) of the study population. Notwithstanding the relatively small cell sizes, affirmative responses to the question regarding feelings of genital arousal were significantly higher among the women 34 years or older after bremelanotide treatment compared with placebo treatment ($P = 0.0339$), while no difference was detected in response among women less than 34 years of age ($P = 1.000$) (Table 3). Similarly, a significantly higher level of sexual desire was reported by women 34 years or older following bremelanotide treatment compared with placebo treatment ($P = 0.0082$), while women younger than 34 years of age showed little difference in their subsequent level of desire according to treatment ($P = 0.5637$).

When age was included in the model as a covariate of the VPA response to the erotic video, no significant differences were found after bremelanotide treatment compared with placebo treatment.

Individual Interviews

In an effort to obtain subjective, qualitative information from subjects regarding their in-clinic and at-home experience following treatment with bremelanotide, in-depth, unblinded interviews were conducted by a professional moderator with 13 subjects on a volunteer basis, depending on subject interest and availability to participate. A summary of these interviews was generated by an independent rater in order to highlight trends that were not captured as part of the study-specific evaluations. Eleven of the 13 subjects interviewed had recorded, per the Treatment Satisfaction Questionnaire, an increase in feelings of sexual desire and/or arousal during the 24 hours following bremelanotide treatment. In general, subjects reported recognition of genital arousal within 10–45 minutes after bremelanotide administration, lasting for some subjects for up to 10 hours, and observations were frequently noted that the intensity of arousal was comparable to, or perhaps greater than that experienced prior to the onset of FSD. Six of the subjects interviewed had reported, per the Treatment Satisfaction Questionnaire, engaging in sexual activity within 24 hours following bremelanotide administration, and five of the six subjects indicated they initiated the encounter with their partners. All five subjects noted that since the onset of FSD, it had been markedly atypical for them to initiate sex with their partners. Most of the subjects who reported arousal and/or desire following bremelanotide treatment, but who did not engage in sexual activity, attributed this to unavailability of a partner. Overall, most women remarked that the quality of the sexual experience following bremelanotide treatment was either comparable to, or better than that experienced prior to the onset of FSD, and, importantly, that it was better than sexual encounters experienced since the onset of FSD.

Safety

Single intranasal doses of 20 mg bremelanotide were safely administered to FSD subjects and were well-tolerated overall. The most common adverse events reported were nausea (5/18, 27.8%) and headache (3/8, 16.7%). Nasal congestion and emesis were reported by one subject each (5.6%). All adverse events were mild in nature, with the exception of one subject who experienced moderate nausea, and all adverse events resolved without treatment or intervention. The frequency and intensity of treatment-emergent adverse events in this study were comparable to what has been observed after administration of 20 mg bremelanotide to men [30]. Compared with pre-dose assessments, no clinically significant changes in blood pressure, heart rate, physical examination, clinical laboratory values, or ECG evaluations were observed.

Discussion

Despite the prevalence of FSD and its impact on quality of life in women, there is a paucity of data on the pathophysiology or treatment of this disor-

der, and relatively few potential pharmacological therapies for FSD have been evaluated in the clinical setting. Thus, there are limited therapeutic options, and medical management of FSD is largely restricted to unapproved hormone therapy and/or counseling.

Evaluation of women's sexual response in clinical settings is intrinsically challenging and necessarily limited in the ability to measure the psychological, situational, and relationship variables that may interact with organic disease factors or comorbidities to produce various symptoms and degrees of severity of FSD [42]. Measurement of vaginal vasocongestion in response to treatment has been analyzed as in-clinic data and as a surrogate physiological marker of genital arousal. However, in women, there is generally poor correlation between subjective sexual arousal and objective (measured) genital blood flow in laboratory settings [22,34,35,43]. In fact, studies reported by Chivers and Bailey [44] reveal that, in contrast to men, discordance between genital arousal and subjective arousal is a consistent finding in women. Subjective sexual arousal is a critical variable to evaluate in this research as improvement of the personal sexual experience is the ultimate goal of treatment. Few instruments, however, have been validated to assess subjective sexual experience, particularly in attempting to discriminate a specific treatment effect in women.

This exploratory study was undertaken to investigate a potential role for bremelanotide in eliciting arousal and/or desire in premenopausal women diagnosed with FSAD. Although there was no evidence to suggest that bremelanotide would necessarily affect vaginal vasocongestion, measurement of vaginal blood flow was included as one of several variables in this pilot study. Not unexpectedly, no difference in vaginal vasocongestion could be attributed to bremelanotide treatment during the time subjects viewed neutral vs. erotic videos. Investigative questionnaire evaluations were employed to monitor the potential effect of bremelanotide, compared with placebo, on several subjective parameters related to the female sexual response. Responses to the questionnaire that queried the at-home experience during the 24-hour post-dose period indicated that bremelanotide had a positive effect on several aspects of perceived level of desire and arousal. The lack of correlation between physiological (VPA) and subjective (questionnaire) outcome measures is neither unusual nor unexpected [22,34,35,43,44].

One limitation in interpretation of these results is that reports of subjective sexual arousal and desire following bremelanotide and placebo treatment were made in the context of having recently viewed erotic visual stimuli. The design of this pilot study did not allow for measurement of the video effect alone or for the effect of bremelanotide in the absence of visual stimulation. In addition, the small sample size precludes meaningful correlations between factors that emerged in history-taking (e.g., the presence of problems in the current relationship and/or current life context or the woman's sexual or nonsexual past) and subject response to bremelanotide. This is, nonetheless, an issue of fundamental importance, and future studies with larger sample sizes are needed to examine potential relationships between etiological factors and response to treatment.

Follow-up interviews revealed that, in many cases, desire and/or arousal persisted for several hours. Pharmacokinetic studies have demonstrated a median time to maximum bremelanotide plasma concentration of approximately 30 minutes and a half-life ($t_{1/2}$) of approximately 2 hours [30]. Male subjects have reported erectile activity that initiated at approximately 45 minutes after dosing and lasted intermittently for up to 12 hours after dosing (unpublished data, Palatin Technologies, Inc.). Reports by several subjects in the current study that desire and arousal were first noticed within 45 minutes post dose and were experienced for up to 10 hours post dose are consistent with experiences reported by men, and lead to the hypothesis that the plasma $t_{1/2}$ may not be the best indicator of bremelanotide's potential duration of action.

Several women also reported during follow-up interviews that they initiated sex with their partners following their in-clinic bremelanotide dose, and that their sexual experience was highly satisfying and comparable to pre-FSD levels of sexual satisfaction. Importantly, subjects noted an improved quality of their sexual encounter after bremelanotide dosing as compared with their sexual experiences since the onset of FSD.

Secondary analyses showed that increased desire and arousal levels following bremelanotide administration were reported more often by subjects 34 years of age or older, as compared with the younger women aged 22–33 years. Although the mean scores of the arousal and desire domains from the FSFI were slightly lower for the older subjects, compared with the younger cohort (1.83 and 2.10 compared with 2.06 and 2.18,

respectively), the differences were not statistically significant. Additionally, the mean scores for the remaining FSFI domains did not differ significantly between the older and younger cohorts. All of the women in the younger group and 7 of the 10 women in the older group were taking hormonal contraceptives for birth control, while 3 of the 10 women in the older group had undergone bilateral tubal ligation. However, the absence of exogenous hormones in the older group does not appear to account for the higher response rate to questions regarding arousal and desire after bremelanotide administration as only one of the three women in the older group who had undergone bilateral tubal ligation reported higher levels of arousal and desire following bremelanotide treatment. It should be noted, however, that in these three women serum testosterone levels likely differed between treatment sessions given that these sessions were scheduled no more than 7 days apart. In future studies, treatment sessions should be scheduled to minimize potential disparities in hormone levels. Measurement of serum hormone levels prior to each session is recommended as well.

As expected, the women in the 34 years and older group had lower levels of sex hormone-binding globulin and total testosterone at screening compared with the women younger than 34 years of age (Table 1); however, all levels were within the normal range. It is noted, though, that the small size of the groups is a major limitation in interpreting these results. Additionally, total serum testosterone levels were measured by radioimmunoassay, and this is not currently considered the most reliable and accurate method of measurement. Other factors, such as the quality of the couple's relationship in determining differences in the patterns of desire and arousal in these cohorts of women, require further elucidation. Future research is also needed to determine the risk–benefit profile related to long-term use of melanocortin receptor agonists, including any potential effects of these agents on food intake and body weight. Endogenous melanocortins are involved in a wide range of physiological functions, including pigmentation, steroidogenesis, energy homeostasis, exocrine secretion, sexual function, analgesia, inflammation, immunomodulation, temperature control, cardiovascular regulation, and neuromuscular regeneration [45]. In particular, evidence suggests a central role for MC3R and MC4R in the regulation of feeding behavior and energy metabolism [45].

Conclusion

The promising insights obtained from this study are preliminary and additional systematic studies are required to confirm a potential role for bremelanotide as a treatment (including combining bremelanotide with psychosocial approaches) for FSD [46,47]. While arousal and desire disorders are classified as discrete subtypes, the responses were highly correlated in this study. Although distinction between desire and arousal disorder may be academically significant, treatment satisfaction for women complaining of FSD may reflect recognition of overlapping and interactive aspects of these disorders. An at-home study designed to assess an effect of bremelanotide on the frequency of satisfying sexual experiences reported, the degree of personal distress realized by FSD, and other variables will be the focus of further research.

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Conflict of Interest: Lisa E. Diamond, Dennis C. Earle, and Ronald Harning are employees of Palatin Technologies.

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