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Effect of Self-Administered Bremelanotide on Sexual Interest and Desire in Premenopausal Women With Female Sexual Dysfunctions

Anita H. Clayton, PhD[1]; Jeffrey Edelson, MD[2]; Robert Jordan, BSc, PMP[2] | [1]University of Virginia, Charlottesville, VA; [2]Palatin Technologies, Inc., Cranbury, NJ

Accepted Abstract

Introduction: The Sexual Interest and Desire Inventory-Female (SIDI-F) is a validated clinician-administered instrument designed to assess the severity of hypoactive sexual desire disorder (HSDD) in women. Bremelanotide (BMT), a novel melanocortin-receptor-4 agonist, is being developed as a treatment for female sexual dysfunction (FSD).

Hypothesis: BMT improves sexual interest and desire in women with FSDs as assessed by the 13-item SIDI-F.

Methods: After screening and a single-blind (SB) placebo, at-home, self-dosing month, premenopausal women with FSDs were randomized to double-blind (DB) placebo or BMT for 12 weeks of at-home self-dosing. Exploratory efficacy measures were analyzed using the SIDI-F which was completed during each of the prescribed clinic visits. A threshold score of 33 is associated with 94.7% sensitivity and 93.4% specificity for severity of HSDD.

Results: Of 1,142 screened subjects, 397 were randomized and 327 completed 1 month of DB study-drug use at home. The change from baseline (SB period) to end of study in the total SIDI-F score was significantly greater with BMT 1.75 mg vs placebo (8.5 vs 4.7, respectively; P=0.0219). Additionally, the increase with BMT 1.75 mg relative to placebo was significantly greater for scores related to desire frequency (item 4; 0.9 vs 0.5, BMT vs placebo; P=0.0480), arousal frequency (item 10; 0.5 vs 0.2, BMT vs placebo; P=0.0474), arousal ease (item 11; 0.7 vs 0.3, BMT vs placebo; P=0.0018), arousal continuation (item 12; 0.4 vs 0.1, BMT vs placebo; P=0.0247), and orgasm (item 13; 1.0 vs 0.4, BMT vs placebo; P=0.0173). Differences between BMT and placebo trended toward significance in scores related to affection (item 5; 0.4 vs 0.1, BMT 1.75 mg vs placebo; P=0.0759) and desire distress (item 7; 0.7 vs 0.4, BMT 1.25 mg vs placebo; P=0.0596). There was no difference between BMT and placebo in the change from baseline in scores for the satisfaction with relationship (item 1), receptivity (item 2), initiation (item 3), desire satisfaction (item 6), thoughts positive (item 8), and erotica (item 9).

Conclusions: The robust efficacy of on-demand treatment with BMT was confirmed using the SIDI-F. The effect was most prominent on SIDI-F items related to desire and arousal. These results corroborate and support previous findings showing a clinically and statistically significant improvement in sexual function with on-demand BMT in women with FSDs.

Discussion: Previously reported data support BMT efficacy in both episodic and monthly recall measurements. Improvement in the desire and arousal aspects of sexual function are the primary drivers of efficacy as demonstrated with the total score SIDI-F. Behavioral patterns such as receptivity, initiation, and thoughts about sex may not show improvement because these items may have been stable upon entry into the study or may take longer to change in response to improvements in desire and arousal.

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References **1.** Clayton AH, Segraves RT, Leiblum S, et al. Reliability and validity of the Sexual Interest and Desire Inventory-Female (SIDI-F), a scale designed to measure severity of female hypoactive sexual desire disorder. *J Sex Marital Ther.* 2006;32(2):115–135. **2.** American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision.* Washington, DC: American Psychiatric Association; 2000. **3.** Clayton AH, Segraves RT, Bakish D, et al. Cutoff score of the sexual interest and desire inventory-female for diagnosis of hypoactive sexual desire disorder. *J Womens Health (Larchmt).* 2010;19(12):2191–2195. **4.** Pfaus JG, Shadiack A, Van Soest T, Tse M, Molinoff P. Selective facilitation of sexual solicitation in the female rat by a melanocortin receptor agonist. *Proc Natl Acad Sci U S A.* 2004;101(27):10201–10204. **5.** Pfaus J, Giuliano F, Gelez H. Bremelanotide: an overview of preclinical CNS effects on female sexual function. *J Sex Med.* 2007;4(suppl 4):269–279. **6.** Diamond LE, Earle DC, Heiman JR, Rosen RC, Perelman MA, 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(4):628–638. **7.** Levine S, Brown C, Palace E, Fischkoff S, Schnorrbusch C. Phase 2B bremelanotide study in pre- and post menopausal women with female sexual arousal disorder. Poster presented at: 56th Annual Clinical Meeting of the American College of Obstetricians and Gynecologists; May 3–7, 2008; New Orleans, LA. Poster 56.

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Introduction

The Sexual Interest and Desire Inventory–Female (SIDI-F)[1] is a validated, clinician-administered instrument designed to assess the severity of hypoactive sexual desire disorder (HSDD)[2] in women. Each of its 13 items contributes to a total score ranging from 0 to 51, with higher scores signifying better sexual function. In North American subjects, a cutoff score of 33 has been associated with 94.7% sensitivity and 93.4% specificity for HSDD diagnosis.[3]

Bremelanotide (BMT) is a novel cyclic heptapeptide that acts as a melanocortin-receptor-4 agonist, with potential downstream effects that may modulate brain pathways involved in sexual response.[4,5] The drug is being developed as a potential treatment for female sexual dysfunctions (FSD).[6,7] In the present trial, subcutaneous self-dosing of BMT on an at-home, as-needed basis was studied in premenopausal women with acquired FSD. Exploratory efficacy measures included the SIDI-F.

Hypothesis

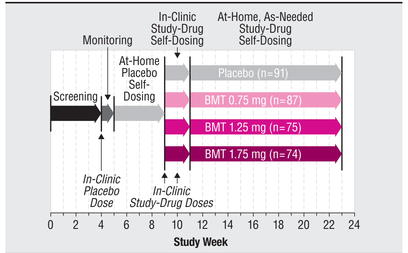
BMT improves sexual interest and desire in women with FSD, as assessed by the 13-item SIDI-F.

Methods

Study Subjects. All subjects were premenopausal women with a ≥6-month duration of HSDD, female sexual arousal disorder (FSAD),[2] or both of these conditions, diagnosed by a qualified clinician using validated instruments and a diagnostic interview. Each subject was in a stable relationship and was willing to be sexually active at least once per month.

Study Design. After a 4-week, no-treatment screening period to confirm their FSD diagnoses, subjects received a single-blind, in-clinic placebo dose, followed by 4 weeks of single-blind, at-home placebo self-dosing (baseline period). Subjects were then randomized to double-blind placebo or BMT 0.75, 1.25, or 1.75 mg, administered as two in-clinic study-drug self-dosings spaced a week apart, followed, a week later, by 12 weeks of at-home, as-needed self-dosing (by pre-filled syringe) ~45 minutes prior to anticipated sexual activity (not exceeding 1 dose per day or 16 doses during a 4-week period). The study design is schematized in Figure 1. The SIDI-F was completed at clinic visits including those scheduled for the end of each at-home self-treatment month. Mean changes from baseline to end of study were assessed for statistical significance (p<0.05) by Van Elteren test, including pre-planned comparisons between placebo and pooled findings for the two highest BMT doses (1.25 and 1.75 mg).

Figure 1. Study Design



Note: At-home placebo self-dosing period=baseline.
BMT, bremelanotide.

Results

Subject Disposition. Of 1,142 screened subjects, 397 were randomized and 327 completed 1 month of double-blind study-drug use at home (thereby comprising the study's modified intent-to-treat [mITT] population).

Subject Characteristics. The baseline characteristics of all double-blind study-drug recipients (the study's safety population) are summarized in Table 1. Overall, 74% had mixed HSDD/FSAD, 23% had solely HSDD, and 3% had solely FSAD. Of the 74% with a mixed diagnosis, 85% had HSDD as their primary diagnosis. Overall, most subjects had regular periods (79%) and were not using oral contraceptives (87%).

Table 1. Subjects' Baseline Characteristics (Safety Population)

Characteristic	Placebo Group (N=97)	BMT Groups 0.75 mg (N=100)	1.25 mg (N=99)	1.75 mg (N=98)	1.25/1.75 mg Pooled (N=197)
Age (years), mean (SD)	37.0 (7.7)	37.6 (7.8)	35.7 (7.2)	37.0 (7.6)	36.4 (7.4)
Race, n (%)					
White	75 (77)	71 (71)	65 (66)	70 (71)	135 (69)
Black	19 (20)	25 (25)	32 (32)	23 (23)	55 (28)
Other	3 (3)	4 (4)	2 (2)	5 (5)	7 (4)
Weight at screening (lbs), mean (SD)	164.4 (42.1)	168.2 (37.9)	174.0 (43.2)	179.2 (45.9)[a]	176.5 (44.5)[b]
BMI at screening (kg/m^2), mean (SD)	27.7 (6.2)	28.5 (6.6)	29.2 (7.1)	29.9 (7.2)[a]	29.5 (7.1)[b]
FSD diagnosis, n (%)					
HSDD	24 (25)	20 (20)	24 (24)	24 (24)	48 (24)
FSAD	4 (4)	3 (3)	3 (3)	2 (2)	5 (3)
Mixed	69 (71)	77 (77)	72 (73)	72 (73)	144 (73)
Menses frequency regular, n (%)	72 (74)	75 (75)	86 (87)	79 (81)	165 (84)
Used oral contraception within the 30 days before screening, n (%)	12 (12)	15 (15)	11 (11)	15 (15)	26 (13)

[a]N=97. [b]N=196.
BMI, body mass index; BMT, bremelanotide; FSAD, female sexual arousal disorder; FSD, female sexual dysfunctions; HSDD, hypoactive sexual desire disorder; SD, standard deviation.

SIDI-F Total Score. In the mITT population, baseline values for SIDI-F total score, and for each SIDI-F item, are summarized in Table 2. Changes from baseline to end of study are summarized in Table 3.

Table 2. Mean (SD) SIDI-F Scores at Baseline (mITT Population, Observed Cases)

Rating (by Item No.)	Placebo Group (N=90)	BMT Groups 0.75 mg (N=85)	1.25 mg (N=74)	1.75 mg (N=68)	1.25/1.75 mg Pooled (N=142)
Total score	21.9 (9.0)	23.9 (9.7)	22.8 (10.9)	21.5 (9.4)	22.2 (10.2)
1. Satisfaction with relationship	1.3 (1.3)	1.5 (1.4)	1.7 (1.4)	1.5 (1.3)	1.6 (1.4)
2. Receptivity	1.7 (1.3)	1.8 (1.2)	1.8 (1.5)	1.5 (1.2)	1.7 (1.4)
3. Initiation	0.9 (0.8)	1.0 (0.8)	0.9 (0.8)	0.9 (0.8)	0.9 (0.8)
4. Desire frequency	1.1 (1.2)	1.4 (1.4)	1.3 (1.3)	1.2 (1.2)	1.3 (1.2)
5. Affection	2.9 (1.2)	3.1 (1.3)	2.8 (1.3)	2.8 (1.3)	2.8 (1.3)
6. Desire satisfaction	1.0 (1.2)	1.4 (1.3)	1.3 (1.4)	1.3 (1.3)	1.3 (1.3)
7. Desire distress	2.5 (1.0)	2.5 (1.1)	2.2 (1.2)	2.4 (0.9)	2.3 (1.1)
8. Thoughts positive	1.7 (1.3)	1.9 (1.4)	2.0 (1.4)	1.7 (1.2)	1.9 (1.3)
9. Erotica	0.7 (0.8)	0.8 (0.7)	0.8 (0.8)	0.7 (0.7)	0.7 (0.7)
10. Arousal frequency	1.6 (0.9)	1.7 (0.9)	1.7 (0.9)	1.6 (0.9)	1.7 (0.9)
11. Arousal ease	1.4 (0.7)	1.4 (0.7)	1.5 (0.8)	1.4 (0.7)	1.4 (0.8)
12. Arousal continuation	1.6 (0.9)	1.7 (0.8)	1.5 (0.8)	1.4 (0.9)	1.5 (0.9)
13. Orgasm	1.4 (1.3)	1.7 (1.3)	1.4 (1.3)	1.2 (1.1)	1.3 (1.2)

BMT, bremelanotide; mITT, modified intent-to-treat; SD, standard deviation; SIDI-F, Sexual Interest and Desire Inventory–Female.

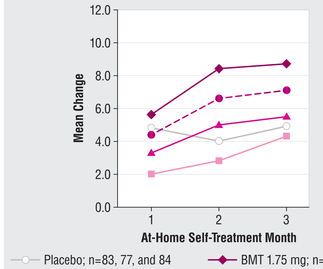
Table 3. Mean (SD) SIDI-F Changes From Baseline to End of Study (mITT Population, Observed Cases)

Rating (by Item No.)	Placebo Group (N=90)	BMT Groups 0.75 mg (N=82)	1.25 mg (N=74)	1.75 mg (N=67)	1.25/1.75 mg Pooled (N=141)
Total score	+4.7 (9.8)	+4.6 (12.4)	+5.9 (9.2)	+8.5 (10.4)*	+7.2 (9.8)
1. Satisfaction with relationship	+0.8 (1.6)	+0.7 (1.6)	+0.7 (1.4)	+1.0 (1.5)	+0.9 (1.4)
2. Receptivity	+0.5 (1.3)	+0.5 (1.5)	+0.6 (1.4)	+0.8 (1.7)	+0.7 (1.6)
3. Initiation	+0.1 (0.9)	+0.2 (1.0)	+0.2 (0.8)	+0.1 (0.9)	+0.2 (0.9)
4. Desire frequency	+0.5 (1.3)	+0.6 (1.7)	+0.6 (1.2)	+0.9 (1.4)*	+0.8 (1.3)
5. Affection	+0.1 (1.2)	+0.3 (1.2)	+0.2 (1.1)	+0.4 (1.1)	+0.3 (1.1)
6. Desire satisfaction	+0.7 (1.5)	+0.5 (1.5)	+0.8 (1.3)	+1.0 (1.5)	+0.9 (1.4)
7. Desire distress	+0.4 (0.9)	+0.3 (1.1)	+0.8 (1.0)	+0.7 (1.1)	+0.7 (1.0)*
8. Thoughts positive	+0.4 (1.3)	+0.3 (1.4)	+0.6 (1.2)	+0.5 (1.3)	+0.5 (1.2)
9. Erotica	+0.3 (0.8)	+0.2 (0.9)	+0.3 (0.8)	+0.3 (0.9)	+0.3 (0.9)
10. Arousal frequency	+0.2 (0.9)	+0.3 (1.1)	+0.2 (0.9)	+0.5 (1.0)*	+0.3 (0.9)
11. Arousal ease	+0.3 (0.8)	+0.2 (1.0)	+0.2 (0.8)	+0.7 (0.8)**	+0.4 (0.8)
12. Arousal continuation	+0.1 (0.9)	+0.1 (1.0)	+0.3 (0.8)	+0.4 (1.0)*	+0.4 (0.9)*
13. Orgasm	+0.4 (1.2)	+0.4 (1.6)	+0.5 (1.2)	+1.0 (1.3)*	+0.7 (1.3)

*p<0.05; **p<0.01; Van Elteren test.
BMT, bremelanotide; mITT, modified intent-to-treat; SD, standard deviation; SIDI-F, Sexual Interest and Desire Inventory–Female.

For total score, the mean change was significantly greater in the BMT 1.75 mg group than in the placebo group (+8.5 versus +4.7; p=0.0219), and trended toward statistical significance at 1.25/1.75 mg pooled (+7.2 versus +4.7; p=0.0828). For each treatment group, Figure 2 displays the mean total-score change by treatment month. At all BMT doses, mean improvement increased throughout the span of at-home self-treatment, and at all time points, the mean changes seen in the BMT groups exhibited dose-dependence.

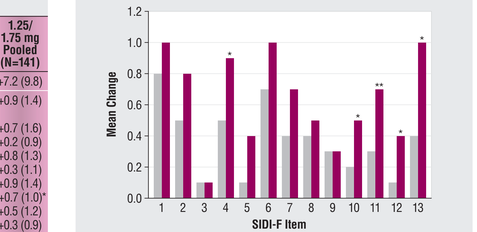
Figure 2. Mean Changes From Baseline in SIDI-F Total Score, by Treatment Group (mITT Population, Observed Cases)



BMT, bremelanotide; mITT, modified intent-to-treat; SIDI-F, Sexual Interest and Desire Inventory–Female.

SIDI-F Items. From baseline to end of study, mean changes in SIDI-F item scores were significantly greater in the BMT 1.75 mg group than in the placebo group for desire frequency (item 4; +0.9 versus +0.5; p=0.0480), arousal frequency (item 10; +0.5 versus +0.2; p=0.0474), arousal ease (item 11; +0.7 versus +0.3; p=0.0018), arousal continuation (item 12; +0.4 versus +0.1; p=0.0247), and orgasm (item 13; +1.0 versus +0.4; p=0.0173). Additionally, the differences between BMT 1.75 mg and placebo trended toward statistical significance for affection score (item 5; +0.4 versus +0.1; p=0.0759). For the 1.75 mg group, Figure 3 displays the mean changes versus placebo in all SIDI-F item scores.

Figure 3. Mean Changes From Baseline in SIDI-F Item Scores, BMT 1.75 mg Versus Placebo (mITT Population, Observed Cases)



*p<0.05; **p<0.01; Van Elteren test.
BMT, bremelanotide; mITT, modified intent-to-treat; SIDI-F, Sexual Interest and Desire Inventory–Female.

At 1.25/1.75 mg pooled, differences between BMT and placebo were statistically significant for desire distress (item 7; +0.7 versus +0.4; p=0.0379) and for arousal continuation (item 12; +0.4 versus +0.1; p=0.0367), and trended toward significance for orgasm score (item 13; +0.7 versus +0.4; p=0.0503).

At 1.25 mg, differences between BMT and placebo trended toward statistical significance for desire distress (item 7; +0.7 versus +0.4; p=0.0596).

Mean changes from baseline to end of study showed no significant differences between BMT and placebo in SIDI-F scores for satisfaction with relationship (item 1), receptivity (item 2), initiation (item 3), desire satisfaction (item 6), thoughts positive (item 8), and erotica (item 9).

Safety. Treatment-emergent adverse events (AEs) reported during double-blind study-drug treatment are summarized in Table 4. At all BMT dosages, the most common AEs were nausea, flushing, and headache, with no marked dose-dependence. Of the 3 BMT users who reported serious AEs (SAEs), each had a history of the same SAE (asthma exacerbation, ventral incisional hernia, noncardiac chest pain) prior to study participation.

Table 4. Reported Adverse Events During Double-Blind Treatment (Safety Population)

Adverse Event, n (% of Group)	Placebo Group (N=97)	BMT Groups 0.75 mg (N=100)	1.25 mg (N=99)	1.75 mg (N=98)	1.25/1.75 mg Pooled (N=197)
Any[a]	49 (51)	64 (64)	61 (62)	67 (68)	128 (65)
Nausea	3 (3)	18 (18)	22 (22)	24 (24)	46 (23)
Flushing	0	17 (17)	14 (14)	17 (17)	31 (16)
Headache	3 (3)	9 (9)	9 (9)	14 (14)	23 (12)
Injection-site pain	3 (3)	6 (6)	6 (6)	7 (7)	13 (7)
Upper respiratory tract infection	4 (4)	8 (8)	5 (5)	4 (4)	9 (5)
Injection-site pruritus	0	4 (4)	4 (4)	6 (6)	10 (5)

[a]The types listed each had an incidence ≥5% among all BMT users.
BMT, bremelanotide.

Sixteen BMT users (5%) and 5 placebo users (5%) had reported AEs leading to withdrawal of double-blind study drug. Among them, 7 subjects (2 BMT 0.75 mg users, 2 BMT 1.75 mg users, and 3 placebo users) were withdrawn for meeting protocol-defined blood-pressure withdrawal criteria mistakenly listed as AEs by the investigator. Accordingly, 12 BMT users (4%) and 2 placebo users (2%) had actual AEs leading to withdrawal of double-blind study drug (Table 5). The types in more than one subject were vomiting (in 4 BMT users), nausea (in 3), and flushing (in 2).

Table 5. Reported Adverse Events Leading to Study-Drug Withdrawal During Double-Blind Treatment (Safety Population)

Adverse Event, n (% of Group)	Placebo Group (N=97)	BMT Groups 0.75 mg (N=100)	1.25 mg (N=99)	1.75 mg (N=98)	1.25/1.75 mg Pooled (N=197)
Any	2 (2)	0	4 (4)	8 (8)	12 (6)
Gastrointestinal disorders	0	0	1 (1)	5 (5)	6 (3)
Vomiting	0	0	1 (1)	3 (3)	4 (2)
Nausea	0	0	0	3 (3)	3 (2)
Diarrhea	0	0	0	1 (1)	1 (<1)
Vascular disorders	0	0	1 (1)	1 (1)	2 (1)
Flushing	0	0	1 (1)	1 (1)	2 (1)
Nervous system disorders	0	0	1 (1)	1 (1)	2 (1)
Headache	0	0	0	1 (1)	1 (<1)
Somnolence	0	0	1 (1)	0	1 (<1)
Respiratory, thoracic, and mediastinal disorders	0	0	2 (2)	0	2 (1)
Cough	0	0	1 (1)	0	1 (<1)
Pharyngeal edema	0	0	1 (1)	0	1 (<1)
General disorders and administration-site conditions	0	0	0	2 (2)	2 (1)
Chest pain	0	0	0	1 (1)	1 (<1)
Injection-site erythema	0	0	0	1 (1)	1 (<1)
Injection-site pain	0	0	0	1 (1)	1 (<1)
Injection-site pruritus	0	0	0	1 (1)	1 (<1)
Psychiatric disorders	0	0	0	2 (2)	2 (1)
Anxiety	0	0	0	1 (1)	1 (<1)
Stress	0	0	0	1 (1)	1 (<1)
Reproductive system and breast disorders	0	0	0	1 (1)	1 (<1)
Genital disorder female	0	0	0	1 (1)	1 (<1)
Vaginismus	0	0	0	1 (1)	1 (<1)
Musculoskeletal and connective tissue disorders	1 (1)	0	0	0	0
Muscle spasms	1 (1)	0	0	0	0
Neoplasms	1 (1)	0	0	0	0
Breast cancer	1 (1)	0	0	0	0

BMT, bremelanotide.

Conclusions

In these SIDI-F findings, subcutaneous BMT self-administered on an as-needed basis by premenopausal women with FSD showed robust efficacy versus placebo, corroborating previous findings of clinically and statistically significant improvements of sexual function in women using on-demand BMT for FSD. Treatment effect was most prominent in SIDI-F items related to desire and arousal. Because baseline was defined as each subject's month of single-blind placebo self-dosing, efficacy was in addition to the substantial placebo effect commonly seen in FSD studies. BMT was generally safe and well tolerated.

Discussion

By episodic measurements (number of satisfying sexual events) and by monthly-recall measurements (Female Sexual Function Index and Female Sexual Distress Scale–Desire/Arousal/Orgasm), previously reported data support BMT efficacy for FSD. Improvement in the desire and arousal aspects of sexual function are the primary drivers of efficacy, as demonstrated here by SIDI-F scores. Patterns in receptivity, initiation, and thoughts about sex may not have shown improvement. However, these items may have been stable at entry into the study or may take longer to change in response to improvements in desire and arousal.

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