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Distress Reduction in Female Sexual Dysfunctions: A Dose-Ranging Study of Subcutaneous Bremelanotide

Sheryl Kingsberg (Presenter),[1] Leonard R. DeRogatis,[2] Jeffrey Edelson,[3] Robert Jordan,[3] Michael L. Krychman[4]

[1]University Hospitals Case Medical Center, Cleveland, OH; [2]Maryland Center for Sexual Health, Lutherville, MD; [3]Palatin Technologies, Inc., Cranbury, NJ; [4]Southern California Center for Sexual Health and Survivorship Medicine, Newport Beach, CA

Introduction

Acquired female sexual dysfunctions (FSD) are common, distressing conditions with a strong negative impact on quality of life.[1-3] 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] Clinical trials have identified efficacy in erectile dysfunction[6,7] and in FSD.[8,9]

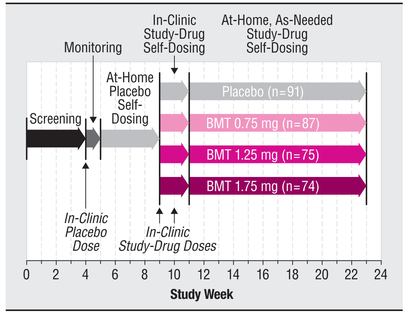
The present dose-ranging study examined the subcutaneous self-administration of BMT on an at-home, as-needed basis by premenopausal women with FSD. The study's pre-planned, prospective efficacy analyses included changes in scores on the Female Sexual Distress Scale–Desire/Arousal/Orgasm (FSDS-DAO).

Methods

Study Subjects. All subjects were required to have a ≥6-month duration of hypoactive sexual desire disorder (HSDD)[10] and/or female sexual arousal disorder (FSAD),[10] diagnosed by a qualified clinician using validated instruments and a diagnostic interview. Each subject was also required to be in a stable relationship and be willing to be sexually active at least once per month.

Study Design. Subjects underwent a no-treatment diagnosis-confirmation month, followed by a single-blind, in-clinic placebo dose and then 4 weeks of single-blind, at-home placebo self-dosing, which constituted the study's baseline period (a novel design devised to address the substantial placebo effect often seen in FSD studies). Subjects were then randomized to double-blind placebo or BMT 0.75, 1.25, or 1.75 mg, self-administered twice as in-clinic doses (a week apart) and then for 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.

Figure 1. Study Design



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

Efficacy Analyses. FSDS-DAO scores were obtained at randomization (baseline) and after 1, 2, and 3 months of at-home study-drug use. Mean score changes from baseline to end of study were analyzed by Van Elteren test, including pre-planned comparisons between findings for placebo and pooled findings for the two highest BMT doses (1.25 and 1.75 mg).

About the FSDS-DAO. The FSDS-DAO is a 15-item questionnaire based on a 13-item instrument, the Female Sexual Distress Scale–Revised (FSDS-R),[11] which was designed to evaluate various aspects of sexual distress over a 30-day recall period. Of the two additional FSDS-DAO questions, one concerns arousal ("How often did you feel…Concerned by difficulties with sexual arousal") and one concerns orgasm ("How often did you feel…Frustrated by problems with orgasm"). All questionnaire responses are on a Likert-type scale ranging from 0 (never) to 4 (always). The total score is the sum of responses, and ranges from 0 to 60; a higher score indicates greater sexual distress. Published evidence supports the test-retest reliability and construct validity of the FSDS-R in women with HSDD,[11] and in the present study's data, the FSDS-DAO demonstrated acceptable internal consistency, test-retest reliability, construct validity, discriminant validity, and responsiveness in women with FSAD and/or HSDD (Palatin data).

Results

Subject Disposition. Of 1,142 screened subjects, 612 were enrolled, 397 were randomized, 394 were exposed to study drug (the study's safety population), and 327 completed 1 month of at-home, double-blind study-drug use and provided efficacy data (the study's modified intent-to-treat [mITT] population). Among them, 287 completed the study.

Subject Characteristics. The baseline characteristics of all safety-population members are summarized in Table 1. Overall, 74% of the subjects 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/m²), 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.

For the mITT population, baseline values of FSD measures are summarized in Table 2. The mean baseline FSDS-DAO total score was 30.5 to 33.3, depending on treatment group. On FSDS-DAO Question 13 ("feeling bothered by low sexual desire"), the mean baseline score was 2.4 to 2.7.

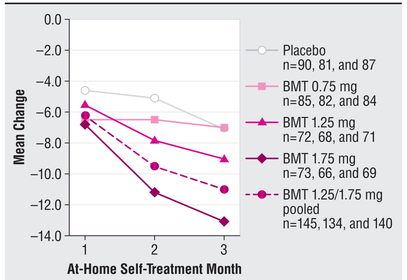
Table 2. FSD Measures at Baseline (mITT Population)

Measure	Placebo Group (N=91)	BMT Groups 0.75 mg (N=87)	1.25 mg (N=75)	1.75 mg (N=74)	1.25/1.75 mg Pooled (N=149)
SSEs during the 4 weeks before randomization					
Mean (SD)	1.7 (1.9)	1.9 (2.1)[a]	1.5 (1.6)	1.8 (2.6)[b]	1.6 (2.1)[c]
Median [range]	1.0 [0–9]	1.0 [0–10]	1.0 [0–8]	1.0 [0–16]	1.0 [0–16]
FSDS-DAO total score					
Mean (SD)	32.1 (12.8)	30.5 (12.4)	32.7 (13.8)	33.3 (12.7)	33.0 (13.2)
Median [range]	31.0 [4–56]	29.0 [7–58]	31.0 [3–60]	35.0 [9–57]	34.0 [3–60]
FSDS-DAO Q13 score					
Mean (SD)	2.6 (1.0)	2.4 (0.9)	2.5 (1.0)	2.7 (0.9)	2.6 (1.0)
Median [range]	3.0 [0–4]	3.0 [0–4]	3.0 [0–4]	3.0 [0–4]	3.0 [0–4]

[a]N=85. [b]N=73. [c]N=148.
BMT, bremelanotide; FSD, female sexual dysfunctions; FSDS-DAO, Female Sexual Distress Scale–Desire/Arousal/Orgasm; mITT, modified intent-to-treat; Q13, Question 13; SD, standard deviation; SSEs, satisfying sexual events.

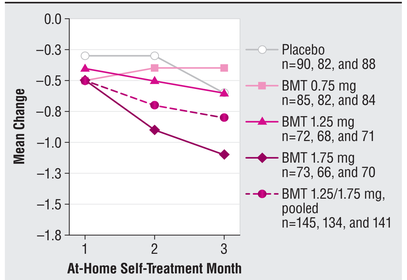
Efficacy Outcomes. For each treatment group, Figure 2 displays the mean change in FSDS-DAO total score seen at each post-baseline time point. For BMT 1.25 and 1.75 mg, the mean improvement increased throughout the overall span of treatment, and after 2 and 3 months, the changes seen in the BMT groups exhibited dose-dependence. Figure 3 displays the mean changes in FSDS-DAO Question-13 subscore. Here, too, the mean improvement at BMT 1.25 and 1.75 mg increased throughout treatment, and after 2 and 3 months, the overall improvement pattern showed dose-dependence.

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



BMT, bremelanotide; FSDS-DAO, Female Sexual Distress Scale–Desire/Arousal/Orgasm; mITT, modified intent-to-treat.

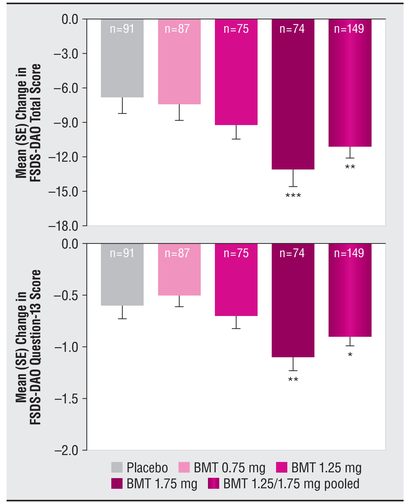
Figure 3. Mean Changes From Baseline in FSDS-DAO Question-13 Score, by Treatment Group (mITT Population, Observed Cases)



BMT, bremelanotide; FSDS-DAO, Female Sexual Distress Scale–Desire/Arousal/Orgasm; mITT, modified intent-to-treat.

Figure 4 displays mean changes at end of study. For FSDS-DAO total score (left bars), the mean (SD) change was –6.8 (13.6) for placebo, versus –7.4 (13.5) for BMT 0.75 mg, –9.2 (10.8) for 1.25 mg, –13.1 (12.9) for 1.75 mg, and –11.1 (12.0) for 1.25/1.75 mg pooled. For FSDS-DAO Question-13 subscore (right bars), the mean (SD) change was –0.6 (1.3) for placebo, versus –0.5 (1.1), –0.7 (1.0), –1.1 (1.2), and –0.9 (1.1) in the BMT groups. On both outcome measures, BMT benefit was statistically significant versus placebo ($p<0.05$) at 1.75 mg and at 1.25/1.75 mg pooled.

Figure 4. Mean Changes (SE) From Baseline to End of Study in FSDS-DAO Total Score and FSDS-DAO Question-13 Score, by Treatment Group (mITT Population)



*$p<0.05$ vs placebo; **$p<0.01$ vs placebo; ***$p<0.001$ vs placebo; Van Elteren test.
BMT, bremelanotide; FSDS-DAO, Female Sexual Distress Scale–Desire/Arousal/Orgasm; mITT, modified intent-to-treat; SE, standard error.

Safety. Treatment-emergent adverse events (AEs) reported during double-blind study-drug treatment are summarized in Table 3. At all BMT dosages, the most common AEs were nausea, flushing, and headache, with no marked dosage-dependence. Of the 3 BMT users who reported serious AEs (SAEs), each had a history of their SAE type (asthma exacerbation, ventral incisional hernia, noncardiac chest pain). None of the SAEs was considered to be related to study drug.

Table 3. 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)
Any leading to withdrawal[b]	5 (5)	2 (2)	4 (4)	10 (10)	14 (7)
Vomiting	0	0	1 (1)	3 (3)	4 (2)
Hypertension[c]	2 (2)	2 (2)	0	1 (1)	1 (0.5)
Nausea	0	0	0	3 (3)	3 (2)
Flushing	0	0	1 (1)	1 (1)	2 (1)

[a]The types listed each had an incidence ≥5% among all BMT users. [b]The types listed each occurred in >1 BMT user. [c]Five subjects (2 on placebo and 3 on BMT) met protocol-defined blood-pressure withdrawal criteria but were incorrectly recorded as having hypertension as an adverse event.
BMT, bremelanotide.

Conclusions

In premenopausal women with FSD, BMT, a non-hormonal agent self-administered subcutaneously on an at-home, on-demand basis, exhibited dose-dependent efficacy for decreasing sexually-related distress, including the distress of feeling bothered by low sexual desire, with statistical significance versus placebo at 1.75 mg and at 1.25/1.75 mg pooled. On both outcomes, the mean improvements among users of 1.25 mg and 1.75 mg increased throughout the study's 3-month duration of at-home, double-blind study-drug use. Because baseline was defined as each subject's month of single-blind placebo self-dosing, efficacy was in addition to the placebo effect commonly seen in FSD studies. BMT was generally safe and well tolerated.

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