50
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Bremelanotide for Hypoactive Sexual Desire Disorder: Analyses From a Phase 2B Dose-Ranging Study

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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 downstream effects that may modulate brain pathways involved in sexual response.[4,5] Clinical feasibility studies have identified potential efficacy in premenopausal and postmenopausal women with FSD.[6,7]

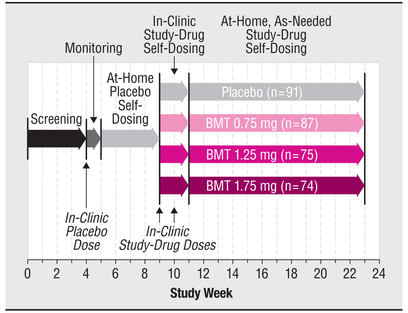
The present study assessed subcutaneous BMT self-dosing in premenopausal women with the most common form of FSD: hypoactive sexual desire disorder (HSDD),[8] female sexual arousal disorder (FSAD),[8] or a combination of both conditions. The study data permitted an exploratory analysis of the subset of subjects with HSDD as their primary diagnosis.

Methods

Study Subjects. All subjects were premenopausal women with a ≥6-month duration of HSDD and/or FSAD diagnosed by a qualified clinician using a diagnostic interview and validated instruments (cutoff total scores of 26.5 on the Female Sexual Function Index [FSFI] and 18 on the Female Sexual Distress Scale–Desire/Arousal/Orgasm [FSDS-DAO]). Each subject was in a stable relationship and was 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 (establishing each subject's baseline). 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 shown in Figure 1.

Figure 1. Study Design



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

Efficacy Analyses. The primary outcome measure was each subject's change from baseline to end of study in the number of satisfying sexual events (SSEs) per month, as recorded by a response of "Yes" to item 10 of the Female Sexual Encounter Profile–Revised questionnaire, which subjects were to complete at home within 24 hours after each sexual encounter. (The item asks, "Did you consider this sexual encounter satisfactory for you?") Key secondary measures included FSFI total score and FSDS-DAO total score. As exploratory analyses, changes on each of the FSD measures were assessed in subjects whose primary FSD diagnosis was HSDD.

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 these 327 subjects, 281 either had solely HSDD (n=75) or had mixed HSDD/FSAD in which the primary diagnosis was HSDD (n=206).

Subject Characteristics. The baseline characteristics of the 340 safety-population members with a primary diagnosis of HSDD are summarized in Table 1. Most had regular periods (77.9%) and were not using oral contraceptives (87.1%). For those in the mITT population, baseline values of FSD measures are summarized in Table 2. By treatment group, the mean number of SSEs during the 4 weeks preceding randomization ranged from 1.5 to 1.9. In all groups, the median number was 1.0.

Table 1. Subjects' Baseline Characteristics (Safety Population)

Characteristic	Placebo Group (N=81)	BMT Groups 0.75 mg (N=87)	1.25 mg (N=87)	1.75 mg (N=85)	1.25/1.75 mg Pooled (N=172)
Age (years), mean (SD)	36.3 (7.7)	37.6 (7.9)	35.9 (7.1)	37.4 (7.6)	36.6 (7.4)
Race, n (%)					
White	66 (81.5)	63 (72.4)	59 (67.8)	64 (75.3)	123 (71.5)
Black	13 (16.0)	22 (25.3)	27 (31.0)	16 (18.8)	43 (25.0)
Other	2 (2.5)	2 (2.3)	1 (1.1)	5 (5.9)	6 (3.5)
Weight at screening (lbs), mean (SD)	162.8 (40.9)	171.7 (38.2)	174.8 (43.0)	174.4 (45.3)[a]	174.6 (44.0)[b]
BMI at screening (kg/m^2), mean (SD)	27.5 (5.9)	29.1 (6.6)[c]	29.3 (7.1)	29.2 (7.0)[a]	29.3 (7.1)[b]
FSD diagnosis, n (%)					
Solely HSDD	24 (29.6)	20 (23.0)	24 (27.6)	24 (28.2)	48 (27.9)
Primarily HSDD, Mixed with FSAD	57 (70.4)	67 (77.0)	63 (72.4)	61 (71.8)	124 (72.1)
Menses frequency regular, n (%)	60 (74.1)	63 (72.4)	75 (86.2)	67 (78.8)	142 (82.6)
Used oral contraception within the 30 days before screening, n (%)	10 (12.3)	11 (12.6)	9 (10.3)	14 (16.5)	23 (13.4)

[a]N=84. [b]N=171. [c]N=85.

BMI, body mass index; BMT, bremelanotide; FSAD, female sexual arousal disorder; FSD, female sexual dysfunctions; HSDD, hypoactive sexual desire disorder; SD, standard deviation.

Table 2. FSD Measures at Baseline (mITT Population)

Measure	Placebo Group (N=76)	BMT Groups 0.75 mg (N=76)	1.25 mg (N=66)	1.75 mg (N=63)	1.25/1.75 mg Pooled (N=129)
SSEs during the 4 weeks before randomization					
Mean (SD)	1.6 (1.8)	1.8 (2.0)[a]	1.5 (1.4)	1.9 (2.7)[b]	1.6 (2.1)[c]
Median [range]	1.0 [0–8]	1.0 [0–9]	1.0 [0–6]	1.0 [0–16]	1.0 [0–16]
FSFI scores, mean (SD)					
Total score	22.2 (6.1)	22.8 (5.6)	21.6 (5.5)	21.5 (4.9)	21.6 (5.2)
Desire subscore	2.4 (1.0)	2.6 (1.1)	2.5 (0.9)	2.3 (0.9)	2.4 (0.9)
FSDS-DAO scores, mean (SD)					
Total score	32.9 (13.0)	31.1 (12.4)	32.5 (14.0)	33.7 (12.3)	33.1 (13.1)
Q13 score	2.6 (1.0)	2.5 (0.9)	2.5 (1.0)	2.7 (1.0)	2.6 (1.0)

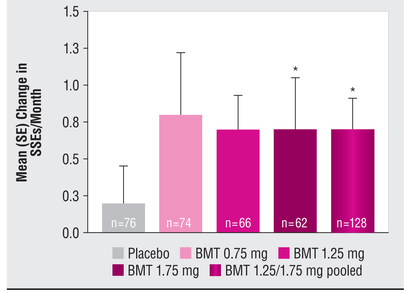
[a]N=74. [b]N=62. [c]N=128.

BMT, bremelanotide; FSD, female sexual dysfunctions; FSDS-DAO, Female Sexual Distress Scale–Desire/Arousal/Orgasm; FSFI, Female Sexual Function Index; mITT, modified intent-to-treat; Q13, Question 13; SD, standard deviation; SSEs, satisfying sexual events.

Efficacy Outcomes. SSE changes are graphed in Figure 2. Among mITT subjects with a primary diagnosis of HSDD, the mean (SD) improvement from baseline to end of study was +0.2 (2.2) SSEs/month for placebo, versus +0.8 (3.6) for BMT 0.75 mg, +0.7 (1.9) for 1.25 mg, +0.7 (2.8) for 1.75 mg, and +0.7 (2.3) for 1.25/1.75 mg pooled.

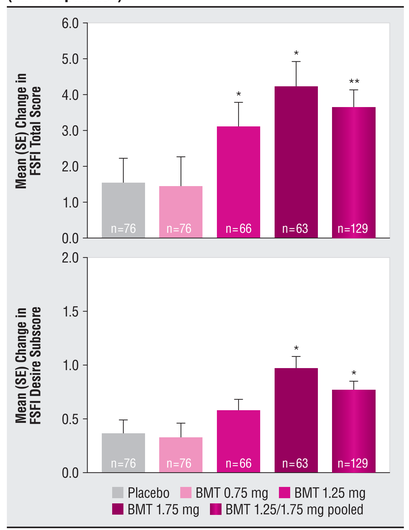
FSFI changes are graphed in Figure 3. The mean (SD) improvement in total score was +1.6 (5.9) for placebo, versus +1.5 (7.2), +3.1 (5.5), +4.2 (5.4), and 3.7 (5.5) in the BMT groups. For FSFI desire subscore, the mean (SD) improvement was +0.4 (1.1) for placebo, versus +0.3 (1.1), +0.6 (0.8), +1.0 (0.9), and +0.8 (0.9) in the BMT groups.

Figure 2. SSE Outcomes, by Treatment Group (mITT Population)



*p<0.05 vs placebo; Van Elteren test.
BMT, bremelanotide; mITT, modified intent-to-treat; SE, standard error; SSEs, satisfying sexual events.

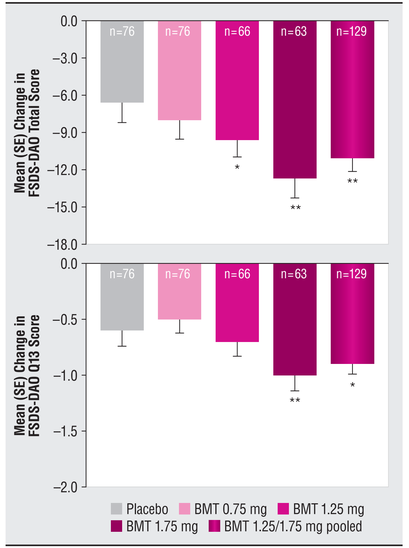
Figure 3. FSFI Outcomes, by Treatment Group (mITT Population)



*p<0.01 vs placebo; **p<0.001 vs placebo; Van Elteren test.
BMT, bremelanotide; FSFI, Female Sexual Function Index; mITT, modified intent-to-treat; SE, standard error.

FSDS-DAO changes are graphed in Figure 4. The mean (SD) improvement in total score was –6.6 (14.1) for placebo, versus –8.0 (13.4), –9.6 (11.2), –12.7 (12.6), and –11.1 (12.0) in the BMT groups. On FSDS-DAO Question 13 ("How often did you feel bothered by low sexual desire" during the preceding 4 weeks, self-rated as 0 ["never"], "rarely" [1], "occasionally" [2], "frequently" [3], or "always" [4]), the mean (SD) improvement was –0.6 (1.2) for placebo, versus –0.5 (1.0), –0.7 (1.0), –1.0 (1.1), and –0.9 (1.1) in the BMT groups.

Figure 4. FSDS-DAO Outcomes, by Treatment Group (mITT Population)



*p<0.05 vs placebo; **p<0.01 vs placebo; Van Elteren test.
BMT, bremelanotide; FSDS-DAO, Female Sexual Distress Scale–Desire/Arousal/Orgasm; mITT, modified intent-to-treat; Q13, Question 13; SE, standard error.

On all outcomes, BMT benefit was statistically significant versus placebo (p<0.05, Van Elteren test) at 1.75 mg and at 1.25/1.75 mg pooled. For FSFI total score and FSDS-DAO total score, benefit was also significant at 1.25 mg.

Safety. Treatment-emergent adverse events (AEs) reported during double-blind study-drug treatment of subjects with a primary diagnosis of HSDD are summarized in Table 3. At all BMT dosages, the most common AEs were nausea, flushing, and headache, with no marked dosage-dependence. AEs that led to withdrawal of double-blind study drug (Table 3) included vomiting, in 4 BMT users (1.5%); nausea, in 3 (1.2%); and flushing, in 2 (0.8%).

Table 3. Reported Adverse Events During Double-Blind Treatment (Safety Population)

Adverse Event, n (% of Group)	Placebo Group (N=81)	BMT Groups 0.75 mg (N=87)	1.25 mg (N=87)	1.75 mg (N=85)	1.25/1.75 mg Pooled (N=172)
Any[a]	41 (50.6)	61 (70.1)	55 (63.2)	61 (71.8)	116 (67.4)
Nausea	1 (1.2)	16 (18.4)	21 (24.1)	22 (25.9)	43 (25.0)
Flushing	0	17 (19.5)	14 (16.1)	15 (17.6)	29 (16.9)
Headache	3 (3.7)	9 (10.3)	9 (10.3)	12 (14.1)	21 (12.2)
Injection-site pain	3 (3.7)	4 (4.6)	6 (6.9)	7 (8.2)	13 (7.6)
Upper respiratory tract infection	3 (3.7)	7 (8.0)	4 (4.6)	3 (3.5)	7 (4.1)
Urinary tract infection	1 (1.2)	6 (6.9)	8 (9.2)	0	8 (4.7)
Any leading to withdrawal[b]	5 (6.2)	2 (2.3)	4 (4.6)	9 (10.6)	13 (7.6)
Vomiting	0	0	1 (1.1)	3 (3.5)	4 (2.3)
Hypertension[c]	2 (2.5)	2 (2.3)	0	1 (1.2)	1 (0.6)
Nausea	0	0	0	3 (3.5)	3 (1.7)
Flushing	0	0	1 (1.1)	1 (1.2)	2 (1.2)

[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.

The impact of BMT on blood pressure and heart rate was characterized in this study by ambulatory blood pressure monitoring initiated before each in-clinic study-drug dose. In general, BMT caused small, transient increases in systolic and diastolic pressures, with an approximate 5% reduction in heart rate during the same time frame.[9]

Conclusions

In premenopausal women with HSDD, BMT self-administered subcutaneously on an at-home, as-needed basis yielded improvements across 5 clinically relevant FSD measures, with robust dose-dependence attaining statistical significance on all measures at 1.75 mg and at 1.25/1.75 mg pooled. Because baseline was defined as each subject's month of single-blind placebo self-dosing, the demonstrated efficacy was in addition to the placebo effect commonly seen in FSD studies. BMT was generally safe and well tolerated.

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