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Bremelanotide for Female Sexual Dysfunctions: Responder Analyses From a Phase 2B Dose-Ranging Study

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Introduction

Acquired female sexual dysfunctions (FSD) encompass a range of conditions classified by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)* as including impairments of sexual desire (hypoactive sexual desire disorder; HSDD) and sexual arousal (female sexual arousal disorder; FSAD).[1] The manual's *Fifth Edition (DSM-5)* proposes that HSDD and FSAD be combined.[2] By any classification system, however, FSD are common and have a strong negative impact on quality of life.[3-5]

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.[6,7] Clinical trials have identified efficacy in erectile dysfunction[8,9] and in FSD.[10,11] In the present trial, subcutaneous self-dosing on an at-home, as-needed basis was studied in premenopausal women with FSD. Key efficacy outcomes were subjected to pre-specified responder analyses anchored to expert recommendations of estimates of minimum clinically important differences (MCIDs).

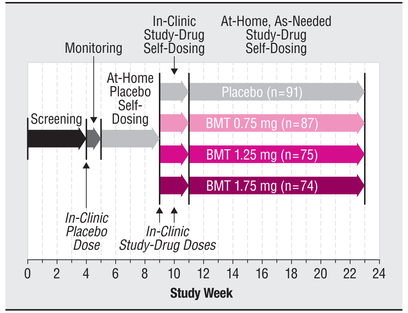
Methods

Study Subjects. All subjects were premenopausal women with a ≥6-month duration of HSDD and/or FSAD 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 screening period to confirm the FSD diagnosis, 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.

Efficacy Analyses. The study's primary efficacy endpoint was each subject's change from baseline to end of study in the monthly number of satisfying sexual events (SSEs), 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).

Figure 1. Study Design



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

Efficacy endpoints also included change in overall sexual function (arousal, desire, etc.), as measured via a 4-week recall period by total score on the Female Sexual Function Index (FSFI), and change in sexual distress, as measured via a 4-week recall period by total score on the Female Sexual Distress Scale–Desire/Arousal/Orgasm (FSDS-DAO). FSFI total score is the sum of the tool's domain scores, and ranges from 2 to 36. Higher scores indicate a greater level of sexual function. FSDS-DAO total score is the sum of the subject's responses, and ranges from 0 to 60. Higher scores indicate greater sexual distress.

For each endpoint, responders were defined as subjects attaining expert estimates of MCIDs: +1 for SSEs per month, +4 for FSFI total score, and –7 for FSDS-DAO total score.

Results

Subject Disposition. Of 1,142 screened subjects, 612 were enrolled and 397 were randomized, 99 to placebo, 100 to BMT 0.75 mg, 99 to BMT 1.25 mg, and 99 to BMT 1.75 mg. Among them, 394 were exposed to study drug, 327 completed 1 month of at-home, double-blind study-drug use and provided efficacy data (for SSEs, 324), and 287 completed the study, 79 on placebo, 77 on BMT 0.75 mg, 66 on BMT 1.25 mg, and 65 on BMT 1.75 mg.

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.

Baseline values of FSD measures among all subjects who provided efficacy data after 1 at-home month (modified intent-to-treat [mITT] population) 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, and the median number in all groups was 1.0.

Table 2. FSD Measures at Baseline (mITT Population)

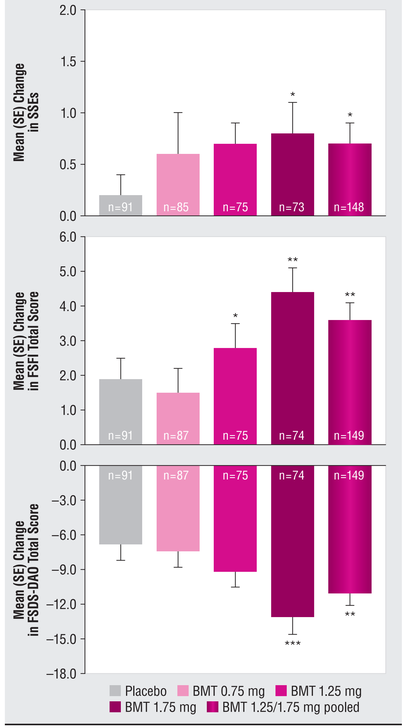
Measure	Placebo Group (N=91)	BMT Groups 0.75 mg (N=87)	1.25 mg (N=75)	1.75 mg (N=74)	1.25/1.75 mg Pooled (N=149)
SSEs during the 4 weeks before randomization					
Mean (SD)	1.7 (1.9)	1.9 (2.1)[a]	1.5 (1.6)	1.8 (2.6)[b]	1.6 (2.1)[c]
Median [range]	1.0 [0–9]	1.0 [0–10]	1.0 [0–8]	1.0 [0–16]	1.0 [0–16]
FSFI total score, mean (SD)	21.9 (5.9)	22.8 (5.4)	21.5 (5.4)	21.7 (5.0)	21.6 (5.2)
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)

[a]N=85. [b]N=73. [c]N=148.

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; SD, standard deviation; SSEs, satisfying sexual events.

Efficacy Outcomes. For the mITT population, Figure 2 displays the mean improvements observed in each treatment group. From baseline to end of study, the mean (SD) change in SSEs per month was +0.2 (2.3) for placebo, versus +0.6 (3.6) for BMT 0.75 mg, +0.7 (1.8) for 1.25 mg, +0.8 (2.9) for 1.75 mg, and +0.7 (2.4) for 1.25/1.75 mg pooled. The mean change in FSFI total score was +1.9 (5.9) for placebo, versus +1.5 (6.9), +2.8 (5.7), +4.4 (5.6), and +3.6 (5.7) in the BMT groups. The mean change in FSDS-DAO total score was –6.8 (13.6) for placebo, versus –7.4 (13.5), –9.2 (10.8), –13.1 (12.9), and –11.1 (12.0) in the BMT groups.

Figure 2. Efficacy Outcomes (mITT Population)

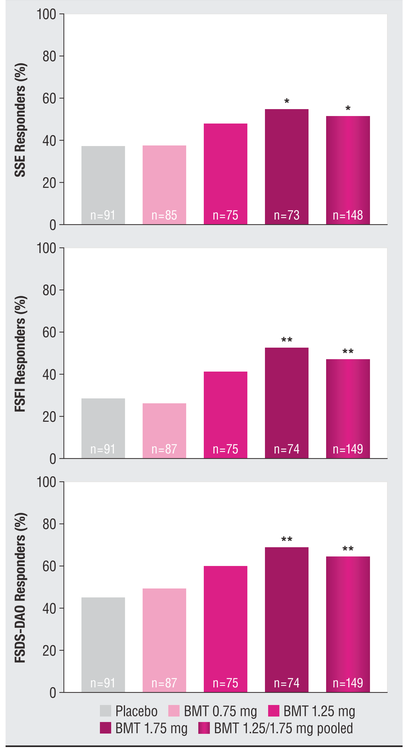


*p<0.05 vs placebo; **p<0.01 vs placebo; ***p<0.001 vs placebo; Van Elteren test.
BMT, bremelanotide; FSDS-DAO, Female Sexual Distress Scale–Desire/Arousal/Orgasm; FSFI, Female Sexual Function Index; mITT, modified intent-to-treat; SE, standard error; SSEs, satisfying sexual events.

For all 3 outcomes, the mean improvements among BMT users attained statistical significance versus placebo (p<0.05, Van Elteren test) at 1.75 mg and for 1.25/1.75 mg pooled. For FSFI total score, the improvement was also significant versus placebo at 1.25 mg. Of note, mean changes from baseline FSFI desire-domain and FSDS-DAO desire-item (Question 13) scores were also statistically significant versus placebo for 1.75 mg.

Responder Analyses. For the mITT population, Figure 3 displays the proportions of subjects who attained the expert-estimated MCID for a given efficacy measure. For SSEs, the proportion was 37% for placebo, versus 38% for BMT 0.75 mg, 48% for 1.25 mg, 55% for 1.75 mg, and 51% for 1.25/1.75 mg pooled. For FSFI, it was 29% for placebo, versus 26%, 41%, 53%, and 47% in the BMT groups. For FSDS-DAO, it was 45% for placebo, versus 49%, 60%, 69%, and 64% in the BMT groups. For all 3 endpoints, the difference from placebo attained statistical significance (p<0.05, Cochran-Mantel-Haenszel test) at 1.75 mg and for 1.25/1.75 mg pooled.

Figure 3. Responder Analyses Anchored to Expert Estimates of MCIDs (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; FSFI, Female Sexual Function Index; MCID, minimum clinically important difference; mITT, modified intent-to-treat; SSEs, satisfying sexual events.

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), and 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 self-administered subcutaneously on an at-home, as-needed basis exhibited dose-dependent efficacy by evaluations with a 28-day recall period, including a decrease in distress and an improvement in overall sexual function, and also episodically, by an increase in the number of SSEs. For each of these efficacy measures, statistical significance versus placebo was seen at 1.75 mg and at 1.25/1.75 mg pooled. For each of these measures, the women also showed dose-dependent increases in responder rates defined by expert-determined MCIDs, with statistically significant differences from placebo 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, efficacy was in addition to the substantial placebo effect commonly seen in FSD studies. BMT was generally safe and well tolerated.

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