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Efficacy of Subcutaneous Bremelanotide Self-Administered at Home by Premenopausal Women With Female Sexual Dysfunction: A Placebo-Controlled Dose-Ranging Study

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Introduction

Female sexual dysfunctions (FSDs) are common, distressing conditions for which no drug therapy is currently approved. The conditions are multifactorial, encompassing low desire, low arousal, orgasmic dysfunction, and/or sexual pain. Bremelanotide is a novel cyclic 7-amino-acid melanocortin peptide that acts as a melanocortin-receptor-4 agonist to presumably modulate brain pathways involved in sexual response. Extensive clinical evidence, using several routes of administration, documents its efficacy in both FSDs and erectile dysfunction.

Aim

To evaluate the efficacy of bremelanotide in a randomized, double-blind (DB), placebo-controlled, parallel-group clinical trial of 3 fixed-dose levels self-administered subcutaneously (SC) on an at-home, as-needed basis by premenopausal women with FSDs.

Methods

All subjects had hypoactive sexual desire disorder (HSDD), female sexual arousal disorder (FSAD), or a combination of these disorders, with at least 6-month duration, diagnosed by a qualified clinician using validated instruments and a diagnostic screening guide. Each subject was in a stable relationship and was willing to be sexually active at least once per month.

The study design is schematized in Figure 1. After 4-week screening, each subject received a single-blind, in-clinic placebo dose, followed by 1-week monitoring and then 4 weeks of single-blind, at-home placebo self-dosing. Subjects were then randomized to DB placebo or bremelanotide 0.75, 1.25, or 1.75 mg. The DB treatment comprised 2 in-clinic study-drug doses spaced a week apart, followed, a week later, by 12 weeks of at-home self-dosing (by pre-filled syringe) ~45 minutes prior to sexual activity (not exceeding 1 dose per day or 16 doses during a 4-week period).

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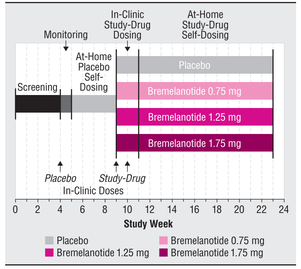
Figure 1. Study Design



Main Outcome Measures

The primary efficacy endpoint was each subject's change, from DB baseline to end of study (EOS), in the number of satisfying sexual events (SSEs) during the 28 days preceding these time points, as recorded by a response of "Yes" to item 10 of the Female Sexual Encounter Profile–Revised questionnaire (to be completed at home within 24 hours after each sexual encounter). The key secondary endpoints were change from DB baseline to EOS in arousal and desire, as measured by total score on the Female Sexual Function Index (FSFI), and in sexual distress, by total score on the Female Sexual Distress Scale–Desire/Arousal/Orgasm (FSDS-DAO).

Results

Of 1,142 screened subjects, 612 were enrolled and 397 were randomized, 99 to placebo, 100 to bremelanotide 0.75 mg, 99 to bremelanotide 1.25 mg, and 99 to bremelanotide 1.75 mg. Among randomized subjects, 327 completed 1 month of DB study-drug use at home (composing the modified intent-to-treat [mITT] population), and 287 completed the study, 79 on placebo, 77 on bremelanotide 0.75 mg, 66 on bremelanotide 1.25 mg, and 65 on bremelanotide 1.75 mg. The baseline characteristics of all DB study-drug recipients are described in Table 1, and DB-baseline values of the key efficacy measures in the mITT population are summarized in Table 2.

Table 1. Subjects' Baseline Characteristics (Safety Population)

Characteristic	Placebo Group (N=97)	Bremelanotide Groups 0.75 mg (N=100)	1.25 mg (N=99)	1.75 mg (N=98)
Age (years), mean (SD)	37.0 (7.7)	37.6 (7.8)	35.7 (7.2)	37.0 (7.6)
Race, n (%)				
White	75 (77%)	71 (71%)	65 (66%)	70 (71%)
Black	19 (20%)	25 (25%)	32 (32%)	23 (23%)
Other	3 (3%)	4 (4%)	2 (2%)	5 (5%)
Weight at screening (lbs), mean (SD)	164.4 (42.1)	168.2 (37.9)	174.0 (43.2)	179.2 (45.9)[a]
Diagnosis, n (%)				
FSAD	4 (4%)	3 (3%)	3 (3%)	2 (2%)
HSDD	24 (25%)	20 (20%)	24 (24%)	24 (24%)
Mixed	69 (71%)	77 (77%)	72 (73%)	72 (72%)
Menses frequency Regular, n (%)	72 (74%)	75 (75%)	86 (87%)	79 (81%)
Used oral contraception within the 30 days before Visit 1, n (%)	12 (12%)	15 (15%)	11 (11%)	15 (15%)

[a]N=97.
FSAD, female sexual arousal disorder; HSDD, hypoactive sexual desire disorder; SD, standard deviation.

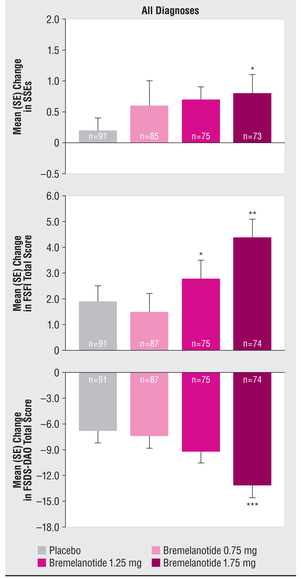
Table 2. Subjects' FSD Measures at DB Baseline (Modified ITT Population)

Characteristic	Placebo Group (N=91)	Bremelanotide Groups 0.75 mg (N=87[a])	1.25 mg (N=75)	1.75 mg (N=74[b])
SSEs during the 28 days before randomization				
Mean (SD)	1.7 (1.9)	1.9 (2.1)	1.5 (1.6)	1.8 (2.6)
Median [range]	1.0 [0–9]	1.0 [0–10]	1.0 [0–8]	1.0 [0–16]
FSFI total score Mean (SD)	21.94 (5.94)	22.75 (5.43)	21.52 (5.42)	21.65 (4.98)
FSDS-DAO total score Mean (SD)	32.1 (12.8)	30.5 (12.4)	32.7 (13.8)	33.3 (12.7)

[a]For SSEs, N=85; [b]For SSEs, N=73.
DB, double-blind; FSD, female sexual dysfunction; FSDS-DAO, Female Sexual Distress Scale-Desire/Arousal/Orgasm; FSFI, Female Sexual Function Index; ITT, intent-to-treat; SSEs, satisfying sexual events.

Efficacy outcomes among users of at least 1 at-home DB study-drug dose are graphed by dosage group in Figure 2. From DB baseline to EOS, the mean (SD) increase in SSEs was 0.2 (2.3) for placebo versus 0.6 (3.6) for 0.75 mg (p=0.4430, Van Elteren test), 0.7 (1.8) for 1.25 mg (p=0.0807), 0.8 (2.9) for 1.75 mg (p=0.0215), and 0.7 (2.4) for 1.25/1.75 mg pooled (p=0.0180). The mean change in FSFI total score was 1.9 (5.9) for placebo versus 1.5 (6.9) for 0.75 mg (p=0.9166, Van Elteren test), 2.8 (5.7) for 1.25 mg (p=0.0279), 4.4 (5.6) for 1.75 mg (p=0.0021), and 3.6 (5.7) for 1.25/1.75 mg pooled (p=0.0017). The mean change in FSDS-DAO total score was –6.8 (13.6) for placebo versus –7.4 (13.5) for 0.75 mg (p=0.5281, Van Elteren test), –9.2 (10.8) for 1.25 mg (p=0.0508), –13.1 (12.9) for 1.75 mg (p=0.0005), and –11.1 (12.0) for 1.25/1.75 mg pooled (p=0.0014). Moreover, FSFI and FSDS-DAO sub-domain results for desire and arousal show statistically significant improvements from baseline among patients receiving 1.75 mg (Figure 3).

Figure 2. Mean (SE) Change in SSEs, FSFI Total Score, and FSDS-DAO Total Score From DB Baseline to EOS Among At-Home Users of DB Study Drug

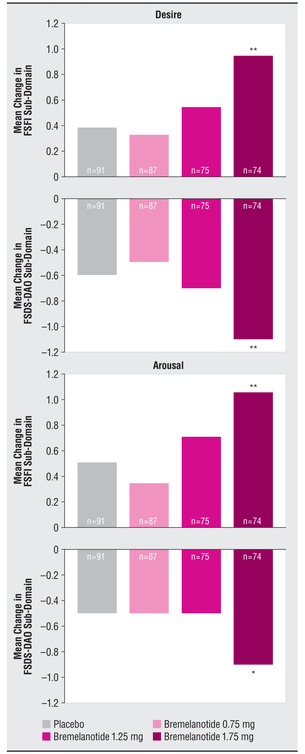


*p<0.05; **p<0.01; ***p<0.001; Van Elteren test.
EOS, end of study; SE, standard error.

Efficacy outcomes are graphed by dosage and FSD diagnosis in Figure 4. On all 3 key endpoints, exploratory analyses demonstrated statistically significant efficacy or a clinically significant trend versus placebo in the HSDD-only and mixed HSDD/FSAD subgroups at 1.25 mg, 1.75 mg, and/or 1.25/1.75 mg pooled.

The data also showed that the mean change from baseline scores with the FSFI and FSDS-DAO were still increasing in the third treatment month (Figure 5). In addition, an exploratory analysis showed a higher percentage of women who were administered bremelanotide (versus placebo) had end-of-study scores for the FSFI and FSDS-DAO total score levels above 26.5 and less than 18, respectively (Figure 6).

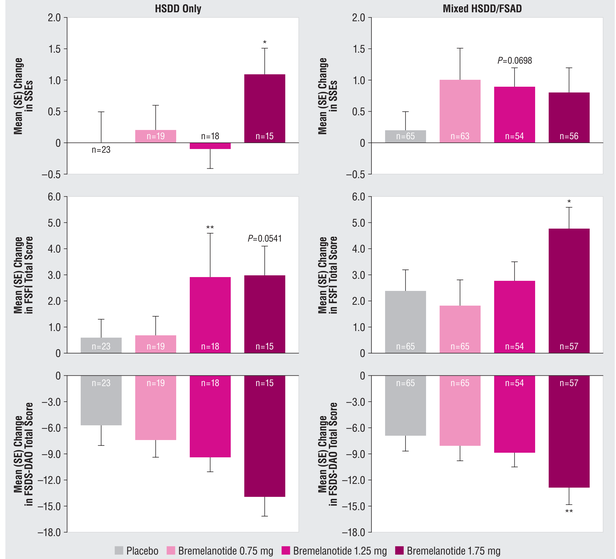
Figure 3. Mean Change in Desire and Arousal Sub-Domains of the FSFI and FSDS-DAO From DB Baseline to EOS Among At-Home Users of DB Study Drug



*p<0.05; **p<0.01; ANCOVA, ANOVA, or Van Elteren test.

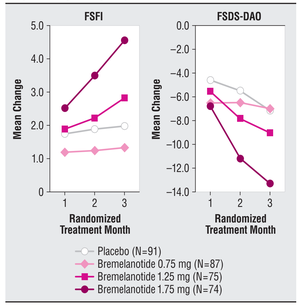
The most common adverse events during DB study-drug treatment (occurring in ≥5% in any group) were nausea, flushing, and headache (Table 3). Drug-treated subjects had ~2mm Hg change in blood pressure (BP), predominantly within 4 hours of dosing; patients meeting the predefined BP withdrawal criteria were evenly distributed among placebo and active arms of the study. Of 7 serious adverse events, none were considered related to bremelanotide treatment.

Figure 4. Mean (SE) Change in SSEs, FSFI Total Score, and FSDS-DAO Total Score From DB Baseline to EOS Among At-Home Users of DB Study Drug With HSDD-Only and With Mixed HSDD/FSAD (Exploratory Analyses)



*p<0.05; **p<0.01; Exact Kruskal-Wallace test (SSEs in the HSDD-only group), Wilcoxon rank-sum test (SSEs in the HSDD/FSAD group and FSFI score in the HSDD-only and HSDD/FSAD groups), or ANCOVA adjusted for baseline, diagnosis, and treatment (FSDS-DAO score in both groups).

Figure 5. FSFI Total Score and FSDS-DAO Total Score Change From Baseline Over Time (Exploratory Analyses)



Conclusions

In premenopausal women with FSDs, bremelanotide self-administered at home at 1.25 and 1.75 mg SC was effective in decreasing distress, increasing arousal and desire, and increasing the number of SSEs, with robust dose response and consistency of effect across all key endpoints. Efficacy was seen in both HSDD and mixed HSDD/FSAD populations. These improvements continued throughout the treatment period, indicating that patients may be able to continue improving after 3 months of treatment. Women receiving bremelanotide were more likely than placebo-treated women to reach key score thresholds for both FSFI and FSDS-DAO. Bremelanotide was generally well tolerated.

Figure 6. Percent of Patients Reaching Key Thresholds for FSFI Total Score and FSDS-DAO Total Score (Exploratory Analyses)

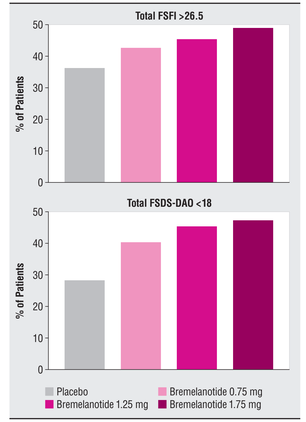


Table 3. Adverse Events During Double-Blind Treatment (Safety Population)

Characteristic	Placebo Group (N=97)	Bremelanotide Groups 0.75 mg (N=100)	1.25 mg (N=99)	1.75 mg (N=98)
Any[a], n (%)	49 (51%)	64 (64%)	61 (62%)	67 (68%)
Nausea	3 (3%)	18 (18%)	22 (22%)	24 (24%)
Flushing	0	17 (17%)	14 (14%)	17 (17%)
Headache	3 (3%)	9 (9%)	9 (9%)	14 (14%)
Injection-site pain	3 (3%)	6 (6%)	6 (6%)	7 (7%)
Upper respiratory tract infection	4 (4%)	8 (8%)	5 (5%)	4 (4%)
Injection-site pruritus	0	4 (4%)	4 (4%)	6 (6%)
Any leading to withdrawal[b], n (%)	5 (5%)	2 (2%)	4 (4%)	8 (8%)
Vomiting	0	0	1 (1%)	3 (3%)
Hypertension	2 (2%)	2 (2%)	0	1 (1%)
Nausea	0	0	0	3 (3%)
Flushing	0	0	1 (1%)	1 (1%)

[a]The types listed are those with incidence ≥5% among bremelanotide users at any dose; [b]The types listed are those that occurred in >1 bremelanotide user across dosing groups.