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Changes in Sexual Functioning in the Bremelanotide RECONNECT Study

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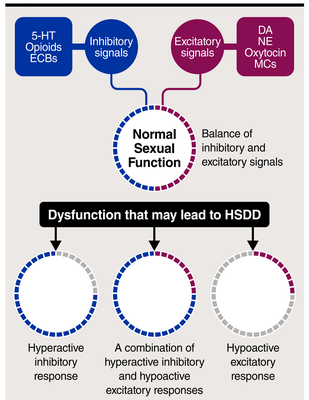
Background

- The most common sexual concern expressed by women is diminished or lack of desire for sexual activity
- When accompanied by distress, this may be diagnosed as hypoactive sexual desire disorder (HSDD), with or without arousal issues[1]
- The etiology of HSDD remains unknown; however, one theoretical model posits that it stems from an imbalance of inhibitory and excitatory signals[2-4] (**Figure 1**)

Figure 1. Excitatory and Inhibitory Pathways Regulating Sexual Response[2]



5-HT, serotonin; DA, dopamine; ECBs endocannabinoids; HSDD, hypoactive sexual desire disorder; MCs, melanocortins; NE, norepinephrine.

- Excitatory signals are regulated by dopamine, norepinephrine, oxytocin, and the melanocortins; inhibitory signals are regulated by serotonin, opioids, and endocannabinoids[3,4]
- Bremelanotide (BMT; PT-141) is an investigational, novel cyclic 7-amino acid melanocortin-receptor agonist with high affinity for the type-4 receptor[5]
- As an analog of the naturally occurring peptide α-melanocyte-stimulating hormone, BMT acts on the physiological and neurobiological components of female sexual function, with the potential to modulate brain pathways involved in sexual desire and arousal in women with HSDD[6]
- BMT is currently being evaluated for the treatment of HSDD (with or without decreased arousal) in premenopausal women

Objectives

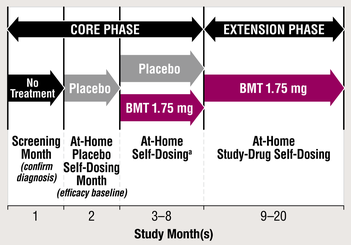
- Two Phase 3 studies assessed the efficacy and safety of a 1.75-mg dose of BMT administered on an as-desired basis for the treatment of HSDD. Here we present the secondary efficacy results

Methods

Study Design

- The RECONNECT study comprises 2, identical, randomized, Phase 3, placebo-controlled, multicenter trials: NCT02333071 (Study 301) and NCT02338960 (Study 302)
- The Core phase of the trials include a 1-month no-drug qualification period (to confirm the diagnosis), followed by a 1-month single-blind placebo-treatment period (to establish baseline), and a 24-week double-blind treatment period. A 52-week open-label extension is ongoing (**Figure 2**)
- Subjects were randomized (1:1) to either placebo or BMT 1.75 mg
- Participants self-administered BMT or placebo subcutaneously via auto-injector as-desired, prior to sexual activity

Figure 2. Study Design



[a]Participants self-administered BMT 1.75 mg or placebo subcutaneously using an auto-injector, as-desired, prior to sexual activity.
BMT, bremelanotide.

Study Participants

- Healthy, premenopausal, nonpregnant women, ≥18 years of age, currently in a stable (≥6 months) relationship
- Diagnosed with HSDD (with/without decreased arousal) for ≥6 months
- Experienced "normal" sexual function in the past for ≥2 years
- Willing to engage in sexual activities ≥1×/month during the study
- Had ***ALL*** of the following at screening:
  - —Patient Health Questionnaire-9 (a screening instrument for depression)[7] total score <10 and score of 0 on question 9
  - —Female Sexual Function Index (FSFI)[8] total score ≤26 (if diagnosed with HSDD with/without symptoms of decreased arousal) ***OR***
  - —FSFI desire domain (FSFI-D) score ≤5 (if diagnosed with HSDD without decreased arousal) regardless of total FSFI score
  - —Female Sexual Distress Scale-Desire/Arousal/Orgasm (FSDS-DAO)[9,10] total score >18
  - —Must have experienced ≥1 satisfying sexual event (SSE) since screening
- The presence of any female sexual dysfunction other than acquired HSDD with or without decreased arousal (eg, lifelong anorgasmia, sexual pain disorder, sexual aversion disorder, primary female sexual arousal disorder) was cause for exclusion

Analysis Population

- The modified intent-to-treat (mITT) analysis population used for the secondary efficacy endpoint analyses was defined as all participants who had used ≥1 dose of the study drug, had FSFI data at baseline, and had ≥1 double-blind follow-up visit.

Secondary Efficacy Assessments

This secondary analysis was assessed based on the results of the following Patient Reported Outcome (PRO) instruments that measure longitudinal and episodic effects of treatment:

- The FSFI is a validated 19-item measure of female sexual function[8] consisting of 6 domains: desire, arousal, lubrication, orgasm, satisfaction, and pain
  - —Arousal, lubrication, and orgasm scores range from 0 to 6
  - —Satisfaction domain score ranges from 0.8 to 6
  - —Total score is the sum of the domain scores and ranges from 2 to 36
  - —The recall period is the previous 4 weeks
  - —Higher scores indicate a greater level of sexual function
- The FSDS-DAO[10] is a validated 15-item instrument based on the 13-item Female Sexual Distress Scale-Revised (FSDS-R)[9]; both questionnaires are designed to evaluate different aspects of sexual-related distress over the past 30 days
  - —Item 13 relates specifically to distress related to low sexual desire
  - —Item 14 relates specifically to difficulty related to sexual arousal
  - —Responses are provided using Likert-type scale and range from 0 (never) to 4 (always)
  - —The total score is calculated as the sum of the responses and ranges from 0 to 60
  - —Higher scores on the FSDS-DAO indicate greater sexual-related distress
- The Female Sexual Encounter Profile-Revised (FSEP-R)[11] is a 10-item measure designed to assess sexual encounters, including initiation, level of desire, satisfaction with arousal, lubrication, arousal, ability to achieve orgasm, and satisfaction with the sexual encounter
  - —Participants completed the FSEP-R within 24 hours after each sexual encounter regardless of whether study drug was used before that encounter
  - —A "sexual encounter" was defined as any act involving sexual contact with genitalia and/or oral mucosa, and included intercourse, oral sex, and masturbation by self or a partner
- The Women's Inventory of Treatment Satisfaction (WITS-9)[12] is a validated instrument that assesses satisfaction with treatment and sexual relations over the previous 4 weeks
  - —Participants answer 9 items on a 7-point numeric rating scale from –3 (very unsatisfied or very likely not to continue) to 3 (very satisfied or very likely to continue)
  - —The total score is calculated as the average of the scores from the 9 questions and ranges from –3.0 to 3.0
  - —Higher scores indicate a higher level of satisfaction with treatment
- General Assessment Questions (GAQ)
  - —The GAQ consists of 4 items related to satisfaction level, including satisfaction with arousal, satisfaction with desire, degree of benefit while on study drug, and impact of taking study drug on relationship with partner
  - —Responses are selected on a 7-point numeric rating scale from 1 (very much worse) to 4 (no change) to 7 (very much better)
  - —GAQ Question #3 asks: Compared to the start of the study (prior to taking the study drug), to what degree do you think you benefited from taking the study drug?
  - —A score ≥5 indicates benefit

Results

Study Population

A total of 1267 women were randomized; 1247 comprised the safety population; 1202 women were included in the mITT population

- Participants were mostly white (84.3% in Study 301; 86.9% in Study 302) and non-Hispanic/Latina (>90% in both studies)
- The safety population included participants who had used ≥1 dose of the double-blind study drug (**Table 1**)
- Baseline scores for FSFI and FSDS-DAO were consistent with a population of women with HSDD (**Table 2**)

Table 1. Baseline Demographics (Safety Population)

Variable	301			302		
	Placebo (n=319)	BMT (n=324)	Total (N=643)	Placebo (n=301)	BMT (n=303)	Total (N=604)
Mean age (SD), y	38.5 (7.2)	38.4 (7.0)	38.5 (7.1)	39.1 (7.0)	38.5 (7.2)	38.8 (7.1)
Mean weight (SD), kg	76.9 (19.6)	78.8 (20.4)	77.9 (20.0)	76.9 (18.2)	78.2 (19.3)	77.6 (18.8)
Mean height (SD), m	1.64 (0.08)	1.65 (0.07)	1.65 (0.07)	1.65 (0.07)	1.65 (0.07)	1.65 (0.07)
Mean BMI (SD), kg/m^2	28.5 (7.3)	28.9 (7.0)	28.7 (7.2)	28.4 (6.5)	28.8 (7.0)	28.6 (6.8)
HSDD Diagnosis, n (%)						
With decreased arousal	240 (75.2)	238 (73.5)	478 (74.3)	206 (68.4)	205 (67.7)	411 (68.0)
Without decreased arousal	79 (24.8)	86 (26.5)	165 (25.7)	95 (31.6)	98 (32.3)	193 (32.0)
Mean number of months since HSDD diagnosis (SD)	49.0 (43.7)	48.3 (42.2)	48.6 (42.9)	45.8 (43.8)	43.7 (42.2)	44.8 (42.9)

BMI, body mass index; BMT, bremelanotide; HSDD, hypoactive sexual desire disorder; SD, standard deviation.

Table 2. Baseline Efficacy Assessments (mITT Population)

Instrument	Baseline Values, mean (SD)			
	Study 301		Study 302	
	Placebo n=316	BMT n=314	Placebo n=290	BMT n=282
FSFI				
Total	19.72 (5.6)	20.0 (5.4)	20.04 (5.4)	20.11 (5.4)
Arousal	2.57 (1.1)	2.64 (1.2)	2.56 (1.1)	2.61 (1.2)
Desire	2.02 (0.8)	2.09 (0.9)	2.05 (0.8)	2.04 (0.8)
Lubrication	4.11 (1.7)	4.20 (1.6)	4.12 (1.6)	4.11 (1.6)
Orgasm	2.95 (1.6)	2.93 (1.6)	3.02 (1.6)	3.11 (1.6)
Satisfaction	2.87 (1.2)	2.87 (1.2)	2.92 (1.2)	2.87 (1.2)
FSEP-R				
Satisfaction with desire (Q4)	1.0 (1.0)	1.0 (1.0)	0.8 (0.8)	0.8 (0.8)
Satisfaction with arousal (Q7)	1.0 (1.0)	1.0 (1.0)	0.9 (0.8)	0.9 (0.8)
% of SSEs rated as satisfactory	42.4	42.5	36.4	38.7
FSDS-DAO				
Total	35.7 (12.1)	35.6 (13.1)	36.9 (12.9)	35.8 (12.7)
Desire (Item 13)	2.84 (0.9)	2.86 (0.9)	2.93 (0.9)	2.86 (0.9)
Arousal (Item 14)	2.6 (1.0)	2.4 (1.1)	2.5 (1.0)	2.5 (1.0)
WITS-9 Total	–0.36 (1.3)	–0.35 (1.3)	–0.30 (1.3)	–0.29 (1.3)

BMT, bremelanotide; FSDS-DAO, Female Sexual Distress Scale-Desire/Arousal/Orgasm; FSEP-R, Female Sexual Encounter Profile-Revised; FSFI, Female Sexual Function Index; mITT, modified intent-to-treat population; PBO, placebo; SD, standard deviation;SSEs; satisfying sexual events; WITS-9, women's index of treatment satisfaction.
The presence of sexual pain was exclusionary.

Primary Efficacy

Both studies met the prespecified coprimary efficacy endpoints among women who completed the study:

- The BMT groups had significantly increased scores on the FSFI-D indicating an increase in desire compared with placebo
- Scores for item 13 of the FSDS-DAO showed a significant reduction in distress related to low sexual desire for women using BMT compared with placebo

NOTE: The primary efficacy results from the RECONNECT study are also being presented at this conference, see: Kingsberg S., et al. Efficacy of Bremelanotide Among Women Completing the Core Phase of The RECONNECT Studies

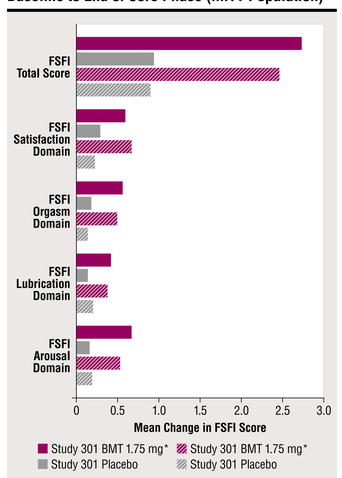
Secondary Efficacy

For the secondary efficacy endpoints, BMT was associated with improved scores and increased satisfaction.

Female Sexual Function Index

- On the FSFI, BMT was also associated with significant improvements in total score, and satisfaction, orgasm, lubrication, and arousal domain scores compared with placebo (**Figure 3**)

Figure 3. Mean Change in FSFI Scores From Baseline to End of Core Phase (mITT Population)

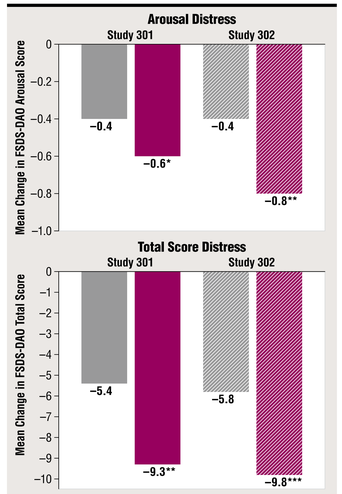


*All BMT scores $P \leq 0.01$; Greater changes mean improvement.
BMT, bremelanotide; FSFI, Female Sexual Function Index; mITT, modified intent-to-treat population.

Female Sexual Distress Scale—Desire/Arousal/Orgasm

- BMT significantly improved distress from arousal and total scores on the FSDS-DAO (**Figure 4**)

Figure 4. Mean Change in FSDS-DAO Arousal[a] and Total Scores: Baseline to End of Core Phase (mITT Population)

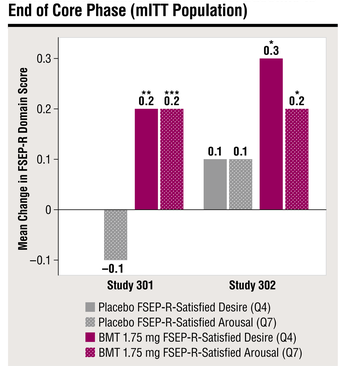


[a]Item 14: "How often do you feel frustrated by difficulties with sexual arousal?"
*P<0.01; **P<0.0001; ***P=0.002.
BMT, bremelanotide; FSDS, Female Sexual Distress Scale; MITT, modified intent-to-treat population.

FSEP-R: Satisfaction with Desire and Arousal

- BMT improved FSEP-R scores for satisfaction with desire and arousal in Study 301. A trend toward significance was seen in Study 302 (**Figure 5**)

Figure 5. Mean Change in the FSEP-R Satisfied Desire and Arousal Domain Scores: Baseline to End of Core Phase (mITT Population)



BMT, bremelanotide; FSEP-R, Female Sexual Encounter Profile-Revised; mITT, modified intent-to-treat population.
*$P \geq 0.09$; **P=0.013; ***P=0.002.

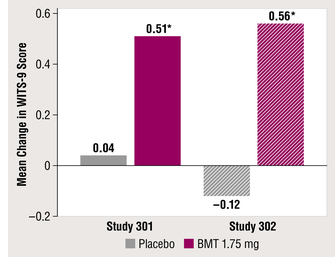
Female Sexual Encounter Profile: Number of Satisfying Sexual Events

- The number of SSEs on the FSEP-R did not differ significantly between treatments in either study
- Women taking BMT reported a higher percentage of these events as sexually satisfactory compared with those taking placebo

Women's Inventory of Treatment Satisfaction-9

- Women taking BMT showed significantly greater improvement in WITS-9 scores compared with placebo, indicating greater satisfaction with treatment and sexual relations (assessed over the previous 4 weeks; **Figure 6**)

Figure 6. Mean Change in WITS-9 Scores at End of Core Phase (mITT Population)



*P<0.0001 for both studies.
BMT, bremelanotide; WITS-9, Women's Inventory of Treatment Satisfaction.

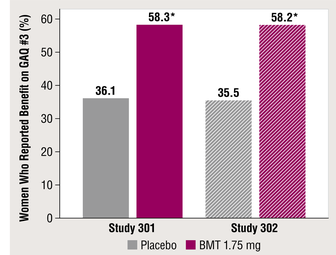
General Assessment Questions

Question #3: Compared with the start of the study (prior to taking the study drug), to what degree do you think you benefited from taking the study drug?

Very much worse			*No Change*			*Very much better*
1	2	3	4	5	6	7

- Women taking BMT reported significantly more benefit from treatment compared with those taking placebo (**Figure 7**)

Figure 7. Percentage of Women Who Reported Benefit[a] on GAQ Question #3 at End of Core Phase (mITT Population)



[a]GAQ #3 score ≥5 indicated benefit; *P<0.0001 for both studies.
BMT, bremelanotide; GAQ, General Assessment Questions.

Safety

- The most common adverse events (AEs) associated with BMT were nausea (39.9%); facial flushing (20.4%); and headache (11.0%)
- Most AEs were mild or moderate in nature
- Treatment-emergent AEs led to treatment discontinuation/interruption in approximately 18% of women taking BMT (vs 2% taking placebo)
- Most of the BMT AEs causing withdrawal were gastrointestinal (11.1% in Study 301 and 7.6% in Study 302)
- BMT's safety profile was favorable and consistent with prior clinical experience with no known interactions with alcohol;[13] no new or unusual safety issues were identified

NOTE: Full safety results from the RECONNECT study are also being presented at this conference, see Kroll R and Lucas J. Bremelanotide is Safe and Well-Tolerated in Premenopausal Women with Hypoactive Sexual Desire Disorder (HSDD): Safety Results From the RECONNECT Studies.

Conclusions

BMT, a self-administered, as-desired, subcutaneous injection, demonstrated robust and consistent efficacy in 2 Phase 3 clinical trials across several domains of sexual function—desire, arousal, lubrication, and orgasm, in premenopausal women.

In addition to statistically significant results in the coprimary endpoints of FSFI-Desire and the FSDS-DAO Item 13 (distress about desire), treatment with BMT was associated with significant improvements in sexual function secondary endpoints in premenopausal women with HSDD, as measured by multiple PRO instruments:

- FSFI arousal, lubrication, orgasm, satisfaction, total scores
- FSDS-DAO arousal and total scores
- FSEP-R desire and arousal scores (for study 301 only)
- WITS-9 score, indicating improved treatment satisfaction and sexual relations
- GAQ question #3, indicating patient-perceived treatment benefit

Change in number of SSEs and FSFI pain scores were not statistically significant

- These endpoints are not key aspects of indication of HSDD
- SSEs "downstream" from robust efficacy seen in desire/distress aspects
- SSEs are least sensitive/specific for detecting efficacy
- Most likely related to inclusion/exclusion criteria impacting baseline data

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