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Bremelanotide is Safe and Well-Tolerated in Premenopausal Women With Hypoactive Sexual Desire Disorder (HSDD): Safety Results From the RECONNECT Studies

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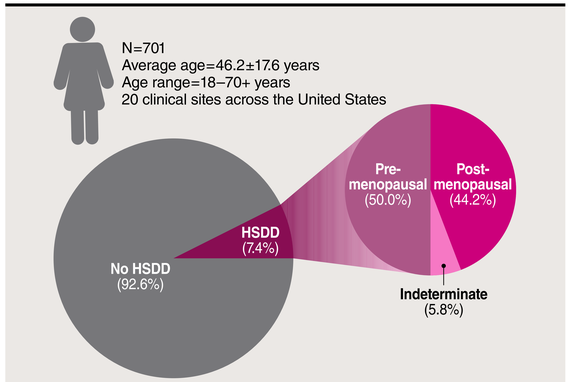
Background

- Female sexual dysfunctions (FSD) includes a range of distressing, multifactorial conditions for which few treatment options exist
- Up to 43% of women aged ≥18 years report having or having had a sexual problem; 12% also report distress associated with their sexual problem (score ≥15 on the Female Sexual Distress Scale [FSDS])[1]
- 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) if it is not a result of another medical condition, drug or medication, or relationship issue
- The overall prevalence of HSDD in the US has been estimated as 7.4%; HSDD is slightly more common among pre- vs postmenopausal women (**Figure 1**)[2,3]
- In the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR), FSD was classified into dysfunctions of desire (eg, HSDD), arousal (eg, female sexual arousal disorder), delay or absence of orgasm, or sexual pain (dyspareunia or vaginismus)[4]
- In the DSM-5, HSDD is included within the diagnostic category of sexual interest/arousal disorder[5]

Figure 1. Prevalence of HSDD



HSDD, hypoactive sexual desire disorder.

- Bremelanotide (BMT; PT-141), is an investigational, novel cyclic 7-amino acid melanocortin-receptor agonist, with high affinity for the type-4 receptor[6]
- 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 improve sexual arousal and desire in women with HSDD[7]
- BMT is being developed as a treatment for HSDD in premenopausal women
- In Phase 2 studies, BMT (1.75 mg) significantly improved female sexual function and sexually satisfying events in women with HSDD as assessed by multiple validated patient-reported outcomes instruments[8]
- The RECONNECT study was designed to evaluate the efficacy and safety of BMT (1.75 mg) for the treatment of HSDD (with or without decreased arousal) in premenopausal women

Objective

- Here we present the results of the safety evaluation of BMT from the double-blind phase of the 2 RECONNECT studies

Methods

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 total score <10 and score of 0 on question 9
  - —Female Sexual Function Index (FSFI) 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) total score >18

Study Design

- The RECONNECT studies comprise 2, identical, 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, followed by a 1-month single-blind placebo treatment period (to establish baseline), and a 24-week double-blind treatment period. Both trials also have an ongoing 52-week open-label Extension phase
- Participants were randomized (1:1) to either placebo or BMT 1.75 mg, self-administered via an auto-injector, as-desired, prior to sexual activity (**Figure 2**)
- The Core phase of the study is complete; the open-label Extension phase is ongoing

Figure 2. Auto-Injector

Safety Assessments

- Safety Assessments included:
  - —Adverse events (AEs)
  - —Vital signs
  - —Electrocardiograms
  - —Clinical laboratory tests

Results

Primary Efficacy

- Both studies met the prespecified co-primary efficacy endpoints, ie, 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 (Study 301 mean change +0.69 vs +0.24; Study 302: +0.80 vs +0.16; both $P<0.0001$)
  - —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 (Study 301 Mean change −0.91 vs −0.34; Study 302: −0.86 vs −0.38 (both $P<0.001$)

Safety

- The safety population (N=1247) includes randomized subjects who had used ≥1 dose of the double-blind study drug
- Participants were mostly white (84.3% in Study 301; 86.9% in Study 302) and non-Hispanic/Latina (>90% in both studies)
- Baseline demographics are shown in **Table 1**

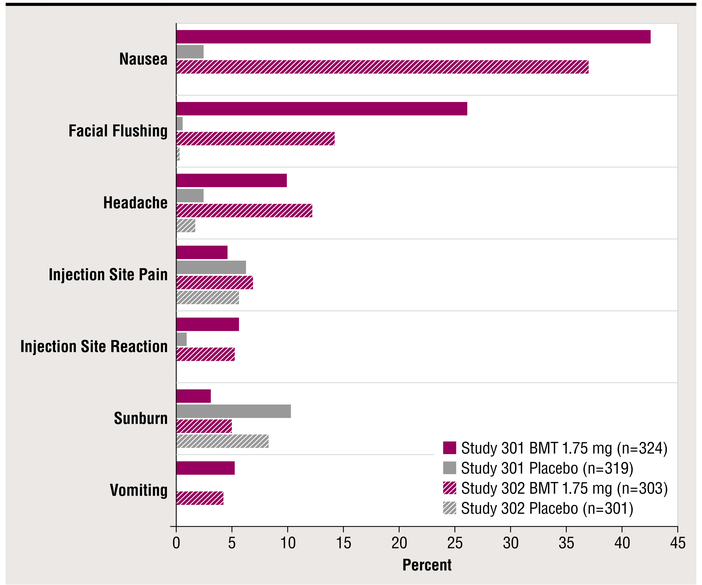
Table 1. Baseline Demographics

	301			302		
Variable	**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)
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; HSDD, hypoactive sexual desire disorder; SD, standard deviation.

- The most frequent treatment-emergent AEs (TEAEs) in the BMT groups were nausea (250 events in 627 patients, 39.9%); facial flushing (128/627, 20.4%); and headache (69/627, 11.0%) (**Figure 3**)

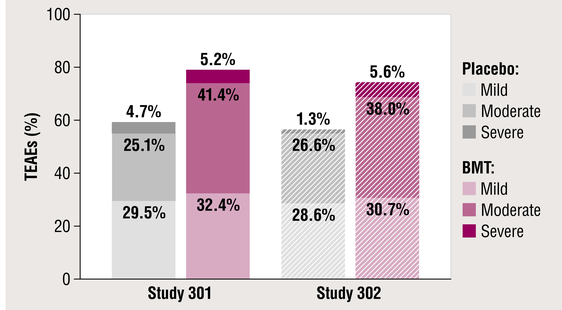
Figure 3. AEs During the Double-Blind Phase With Occurrence of ≥5% In Either Treatment Group for Either Study



BMT, bremelanotide; AEs, adverse events.

- Most TEAEs were mild or moderate in severity (**Figure 4**)
- TEAEs led to treatment discontinuation or interruption in 18.0% of women taking BMT (vs 2.1% for placebo)

Figure 4. Overview of TEAEs by Study, Treatment, and Severity



BMT, bremelanotide; TEAE, treatment emergent adverse event.
AEs considered related to treatment with BMT and assessed as severe (reported >1 time) were nausea, headache, abdominal pain, vomiting, and myalgia; increased blood creatine phosphokinase (CPK; **Table 2**).

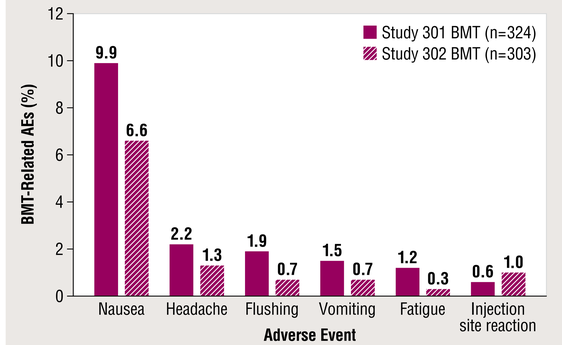
Table 2. Severe AEs with >1 Occurrence in Either Group

	301		302	
AE, n (%)	**Placebo**	**BMT**	**Placebo**	**BMT**
Nausea	0	5 (1.5)	0	8 (2.6)
Headache	0	2 (0.6)	0	3 (1.0)
Abdominal pain	0	0	0	3 (1.0)
Vomiting	0	0	0	2 (0.7)
Myalgia	0	0	0	2 (0.7)
Increased CPK	2 (0.6)	0	0	0

AE, adverse event; BMT, bremelanotide; CPK, creatine phosphokinase.

- The most common BMT AEs (occurring at a rate ≥1%) that led to discontinuation or drug withdrawal during the Core phase are shown in **Figure 5**

Figure 5. Most Frequent BMT-Related AEs (≥1%) Leading to Discontinuation or Drug Withdrawal



AE, adverse event; BMT, bremelanotide.

- There were 2 serious AEs (SAEs) considered related to treatment with BMT in study 301: 1 episode of nausea/vomiting and 1 episode of headache in the same participant; there were no SAEs in study 302
- There were no clinically significant changes in vital signs, clinical laboratory data, or electrocardiograms in either study
- The safety profile of BMT was consistent with prior clinical experience and no new or unusual safety issues were identified

Conclusion

Bremelanotide is a safe, well-tolerated, potential treatment for premenopausal women with HSDD that can be taken 'as desired'. BMT has no known alcohol interactions.[9]

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