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# Efficacy of the Investigational Drug Bremelanotide in the RECONNECT Studies

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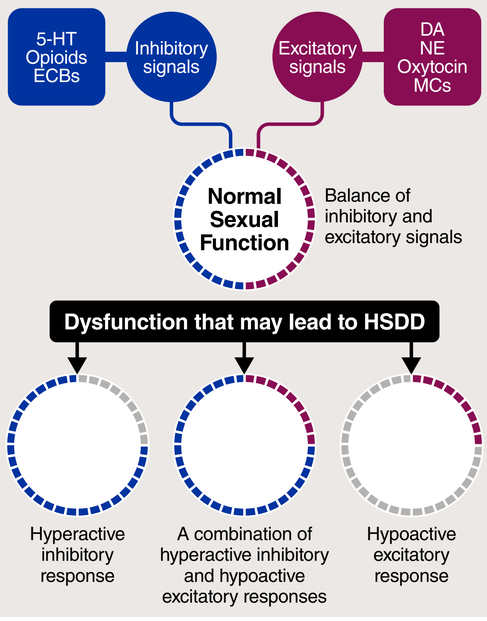
## Background

- 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)[1]
- The etiology of HSDD remains unknown; however, one theoretical model posits that it stems from an imbalance of inhibitory and excitatory signals[2,3]

## Mechanism of Sexual Response

- Excitatory signals are regulated by dopamine (DA), norepinephrine (NE), oxytocin, and the melanocortins (MCs)[3,4]
  - — DA and the MCs stimulate attention and desire
  - — NE and oxytocin stimulate sexual arousal
- Inhibitory signals are regulated by serotonin (5-HT), opioids, and endocannabinoids (ECBs)[3,4]
  - — 5-HT regulates satiety, opioids manage sexual rewards, and ECBs play a role in sedation
- The pathophysiology of HSDD, whether hyperactive inhibition, hypoactive excitation, or a combination, stems from an imbalance of these signals[3,4] (**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.

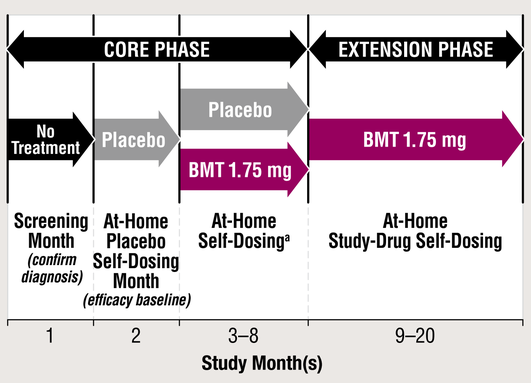
### *Bremelanotide*

- Bremelanotide (BMT; PT-141) is a novel cyclic 7-amino acid MC-receptor agonist, with high affinity for the type-4 receptor[5]
- It is believed that BMT acts on the physiological and neurobiological components of female sexual function, with the potential to modulate brain pathways involved in sexual arousal and desire in women with HSDD[6]
- Among female rats primed with estrogen and progesterone or estrogen alone, BMT significantly increased measures of solicitation without altering pacing or lordosis[7]
- Among premenopausal women with HSDD with or without arousal disorder participating in a Phase 2 study,[8] subcutaneous administration of BMT 1.75 mg resulted in
  - — Significant increase in the number of sexually satisfying events (SSEs) vs placebo when taken prior to sexual activity
  - — Significant increase (improvement) in total and desire domain scores on the Female Sexual Function Index (FSFI)[9,10]
  - — Decrease (less distress) in both the total score and scores on the desire, arousal, and orgasm items of the Female Sexual Distress Scale-Desire/Arousal/Orgasm (FSDS-DAO)[11,12]

### *The RECONNECT Studies*

- The RECONNECT studies comprise 2 identical, randomized, Phase 3, placebo-controlled, multicenter trials (NCT02333071 [Study 301] and NCT02338960 [Study 302]) of BMT administered as-desired for the treatment of HSDD in premenopausal women
- The Core phase of the trials includes a 1-month no-intervention qualification period, a 1-month single-blind placebo treatment period, and a 24-week double-blind treatment period. Both trials also have an ongoing 52-week open-label extension (**Figure 2**)

**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.

## Objectives

### *Primary Efficacy Analyses*

- To evaluate the safety and efficacy of BMT 1.75 mg self-administered, as-desired, for the treatment of HSDD

### *Secondary Efficacy Analyses*

- To evaluate the efficacy of BMT 1.75 mg in the double-blind Core phase, as assessed by participants' responses to questionnaires measuring sexual function, treatment satisfaction, and distress associated with sexual dysfunction

## Study Participants

- Healthy, premenopausal, nonpregnant women, ≥18 years of age, currently in a stable relationship of at least 6 months
- Diagnosed with HSDD (with or without decreased arousal); symptoms present 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[13] (a screening instrument for depression) total score <10 and score of 0 on question 9
  - — 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
  - — FSDS-DAO total score >18
- The presence of any female sexual dysfunction other than acquired HSDD with or without decreased arousal was cause for exclusion

## Key Outcome Measures

### *Co-Primary Efficacy Endpoints*

- Change from baseline to end-of-study (EOS) in the FSFI desire domain score
- Change from baseline to EOS in the score for feeling bothered by low sexual desire, as measured by Item 13 of the FSDS-DAO

### *Secondary Efficacy Outcome Measures*

- FSFI total, arousal, lubrication, orgasm, and satisfaction scores
- FSDS-DAO total and arousal scores
- SSE items from the Female Sexual Encounter Profile-Revised (FSEP-R)[14]
- Women's Inventory of Treatment Satisfaction (WITS-9)[15]
- Question #3 on the General Assessment Questionnaire

## Results

### *Participants and Baseline Demographics*

- The primary efficacy population (mITT) comprises the 1202 women who completed at least 1 month of the Core phase of the study
- Participants were mostly white (>84%) and non-Hispanic/Latina (>90%) in both studies (**Table 1**)

**Table 1. Baseline Demographics (Safety Population[a])**

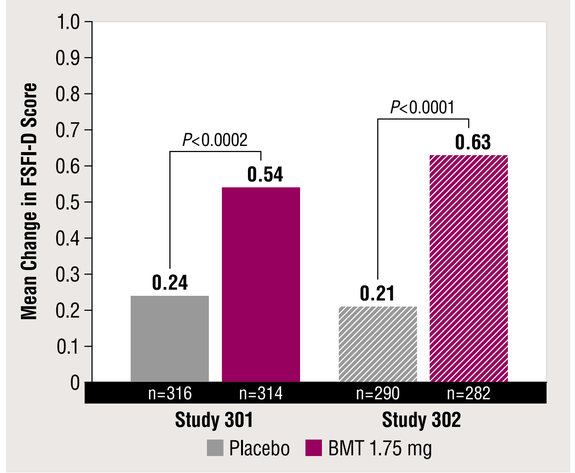
| Variable | Study 301 Placebo (n=319) | Study 301 BMT (n=324) | Study 301 Total (n=643) | Study 302 Placebo (n=301) | Study 302 BMT (n=303) | Study 302 Total (n=604) |
|---|---|---|---|---|---|---|
| Mean age (SD), y | 38.5 (7.2) | 38.4 (7.0) | 38.5 (7.1) | 39.1 (7.0) | 38.5 (7.2) | 38.8 (7.1) |
| Mean 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/m² | 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) |

[a]Participants who had used ≥1 dose of the double-blind study drug.
BMI, body mass index; BMT, bremelanotide; HSDD, hypoactive sexual desire disorder; SD, standard deviation

### *Primary Efficacy (mITT Population)*

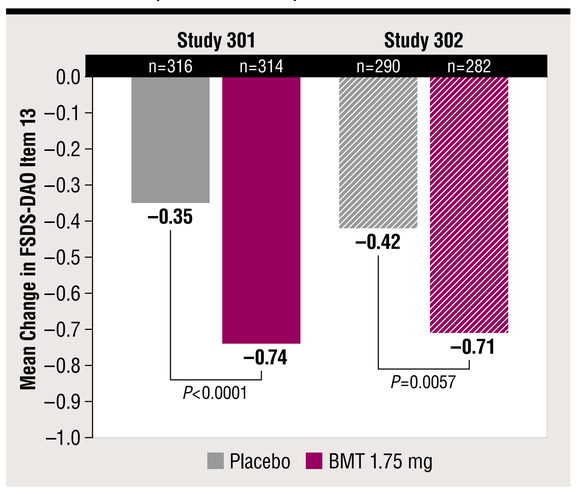
- Compared with women taking placebo, women using BMT had significantly increased scores on the FSFI-D indicating an increase in desire ($P<0.001$; **Figure 3**) and a significant reduction in distress related to low sexual desire on Item 13 of the FSDS-DAO ($P<0.01$; **Figure 4**)

**Figure 3. Change in FSFI-D from Baseline to End of Core (Double-Blind) Phase**




*P* values determined by unadjusted Wilcoxon rank-sum test.
BMT, bremelanotide; FSFI-D, Female Sexual Function Index desire domain.

**Figure 4. Change in FSDS-DAO Item 13[a] from Baseline to End of Core (Double-Blind) Phase**



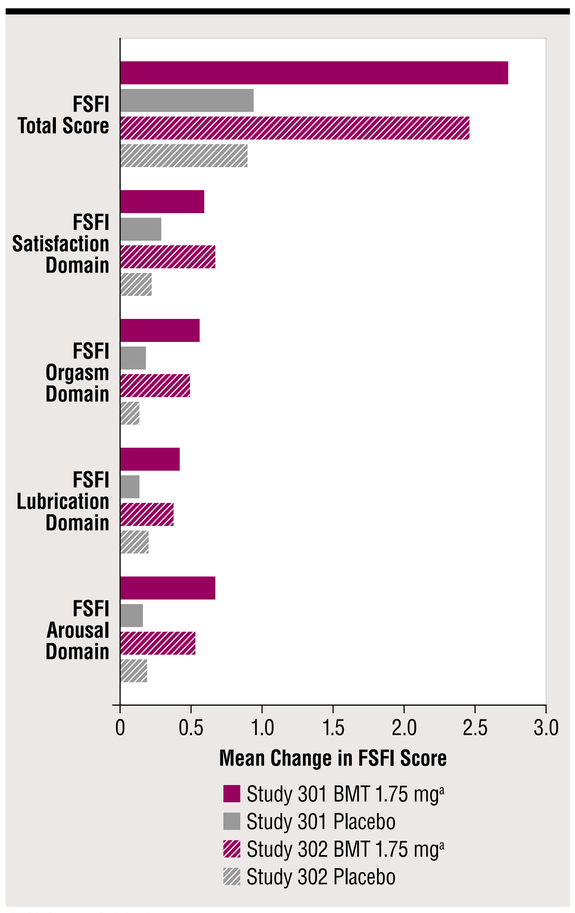

[a]Item 13: "How often do you feel bothered by low sexual desire?" Scores range from 0 to 4 where 0=never; 1=rarely; 2=occasionally; 3=frequently; 4=always.
*P* values determined by unadjusted Wilcoxon rank-sum test.
BMT, bremelanotide; FSDS-DAO, Female Sexual Distress Scale-Desire/Arousal/Orgasm.

### *Secondary Efficacy (mITT Population)*

#### *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 5**)

**Figure 5. Mean Change in FSFI Scores: Baseline to End of Core Phase**

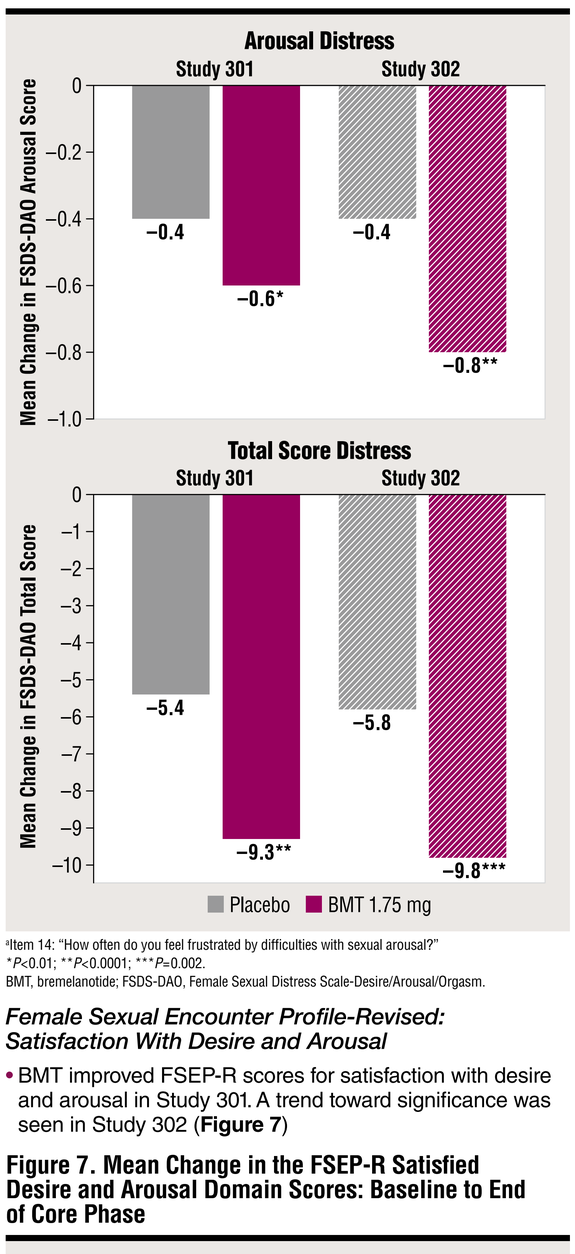



[a]All BMT scores $P\leq0.01$; Greater changes mean improvement.
BMT, bremelanotide; FSFI, Female Sexual Function Index.

#### *Female Sexual Distress Scale-Desire/Arousal/Orgasm*

- BMT significantly reduced the distress from arousal and total scores on the FSDS-DAO (**Figure 6**)

**Figure 6. Mean Change in FSDS-DAO Arousal[a] and Total Scores: Baseline to End of Core Phase**

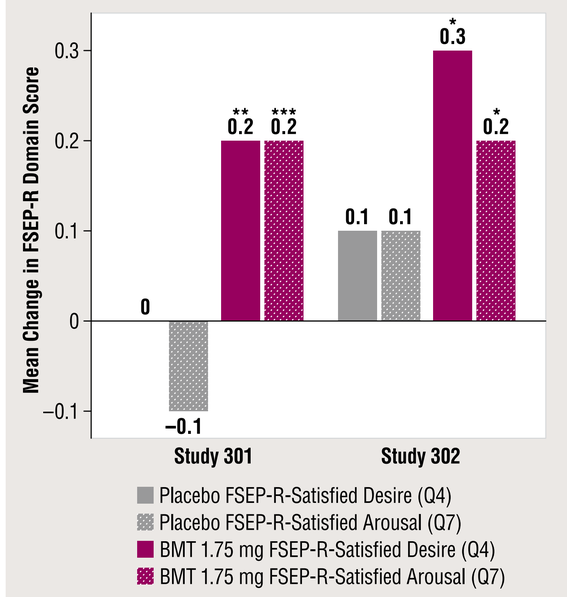



[a]Item 14: "How often do you feel frustrated by difficulties with sexual arousal?"
*$P<0.01$; **$P<0.0001$; ***$P=0.002$.
BMT, bremelanotide; FSDS-DAO, Female Sexual Distress Scale-Desire/Arousal/Orgasm.

#### *Female Sexual Encounter Profile-Revised: 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 7**)

**Figure 7. Mean Change in the FSEP-R Satisfied Desire and Arousal Domain Scores: Baseline to End of Core Phase**




*$P\geq0.09$; **$P=0.013$; ***$P=0.002$.
BMT, bremelanotide; FSEP-R, Female Sexual Encounter Profile-Revised.

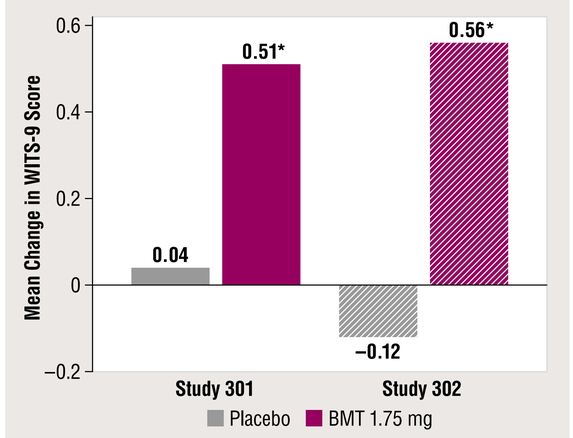
#### *Female Sexual Encounter Profile: Number of Sexually Satisfying Events*

- The change in the number (count) of SSEs did not differ significantly between treatments in either study
- However, women taking BMT reported a significantly higher percentage of events as sexually satisfying 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 8**)

**Figure 8. Mean Change in WITS-9 Scores at End of Core Phase**




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

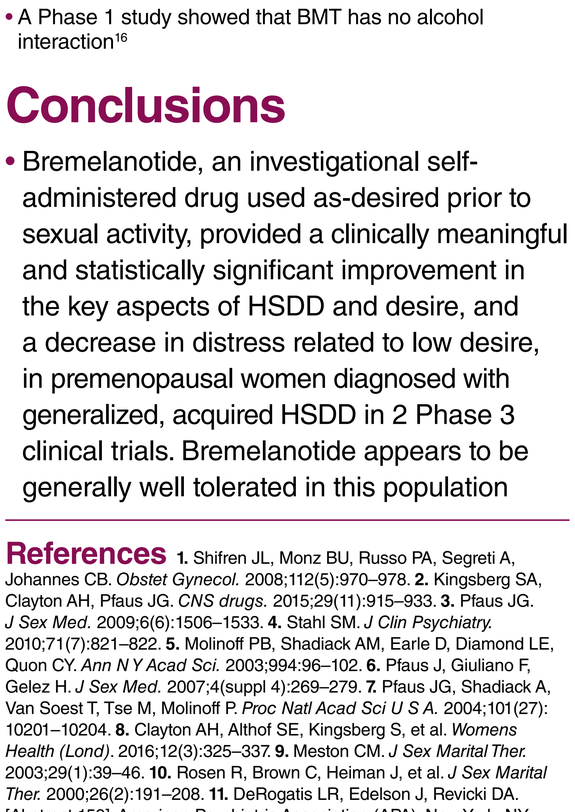
#### *General Assessment Questionnaire*

- 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 9**)

**Figure 9. Percentage of Women Who Reported Benefit[a] on GAQ Question #3 at End of Core Phase**




[a]Score ≥5 indicated benefit; *$P<0.0001$ for both studies.
BMT, bremelanotide; GAQ, General Assessment Questionnaire.

## Safety

- Most adverse events (AEs) were mild or moderate
- Treatment-emergent AEs led to treatment discontinuation/interruption in approximately 18% of women taking BMT (vs 2% for placebo)
- Most of the BMT AEs causing study withdrawal were nausea (9.9% of patients in Study 301; 6.6% in Study 302) and vomiting (1.5% and 0.7% in Studies 301 and 302, respectively)
- BMT's safety profile was consistent with prior clinical trial experience; no new or unusual safety issues were identified for the double-blind period
- A Phase 1 study showed that BMT has no alcohol interaction[16]

## Conclusions

- Bremelanotide, an investigational self-administered drug used as-desired prior to sexual activity, provided a clinically meaningful and statistically significant improvement in the key aspects of HSDD and desire, and a decrease in distress related to low desire, in premenopausal women diagnosed with generalized, acquired HSDD in 2 Phase 3 clinical trials. Bremelanotide appears to be generally well tolerated in this population

**References** **1.** Shifren JL, Monz BU, Russo PA, Segreti A, Johannes CB. *Obstet Gynecol.* 2008;112(5):970–978. **2.** Kingsberg SA, Clayton AH, Pfaus JG. *CNS drugs.* 2015;29(11):915–933. **3.** Pfaus JG. *J Sex Med.* 2009;6(6):1506–1533. **4.** Stahl SM. *J Clin Psychiatry.* 2010;71(7):821–822. **5.** Molinoff PB, Shadiack AM, Earle D, Diamond LE, Quon CY. *Ann N Y Acad Sci.* 2003;994:96–102. **6.** Pfaus J, Giuliano F, Gelez H. *J Sex Med.* 2007;4(suppl 4):269–279. **7.** Pfaus JG, Shadiack A, Van Soest T, Tse M, Molinoff P. *Proc Natl Acad Sci U S A.* 2004;101(27):10201–10204. **8.** Clayton AH, Althof SE, Kingsberg S, et al. *Womens Health (Lond).* 2016;12(3):325–337. **9.** Meston CM. *J Sex Marital Ther.* 2003;29(1):39–46. **10.** Rosen R, Brown C, Heiman J, et al. *J Sex Marital Ther.* 2000;26(2):191–208. **11.** DeRogatis LR, Edelson J, Revicki DA. [Abstract 159]. American Psychiatric Association (APA); New York, NY; May 3–7, 2014. **12.** DeRogatis LR, Rosen R, Leiblum S, Burnett A, Heiman J. *J Sex Marital Ther.* 2002;28(4):317–330. **13.** Kroenke K, Spitzer RL, Williams JB. *J Gen Intern Med.* 2001;16(9):606–613. **14.** Ferguson DM. *J Sex Marital Ther.* 2002;28(suppl 1):77–83. **15.** Corty EW, Althof SE, Wieder M. *J Sex Med.* 2011;8(1):148–157. **16.** Clayton AH, Lucas J, DeRogatis LR, Jordan R. *Clin Ther.* 2017;39:514–526.

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