Exit Survey of Women With Hypoactive Sexual Desire Disorder Treated With Bremelanotide in the RECONNECT Studies Demonstrated Meaningful Treatment Benefits

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Background

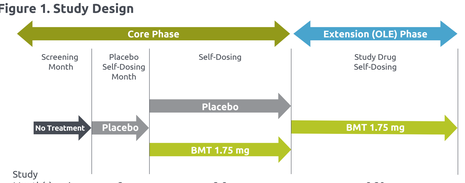
- Female sexual dysfunction (FSD) comprises a group of conditions with physiological, psychological, and social components[1]
- The most common sexual concern expressed by women with FSD is lack of or diminished desire for sexual activity.[2] When accompanied by distress, this may be diagnosed as hypoactive sexual desire disorder (HSDD)[3,4]
  - In an attitudinal survey of women living with low sexual desire, 67% of premenopausal women felt that low desire resulted in less connectedness in their relationships with their partners and 86% had some level of distress about it[5]
- Bremelanotide (BMT), a novel cyclic 7-amino acid melanocortin-4-receptor agonist, with high affinity for MC4R, is an investigational drug currently in development for the treatment of HSDD[6]
  - BMT is taken as desired to improve sexual desire accompanied by a decrease in personal distress in premenopausal women diagnosed with HSDD
- Primary analyses of the RECONNECT studies showed that BMT had robust and consistent efficacy in two phase 3 clinical trials across several domains of sexual function, including desire, arousal, lubrication, and orgasm, in premenopausal women with HSDD[7]
  - BMT was well tolerated, and the most common treatment-related adverse events were nausea, flushing, and headache[8]
- The objective of this survey was to understand the impact of HSDD in premenopausal women and to provide a deeper understanding of the effect and impact/meaningfulness of BMT beyond clinical trial results

Methods

Study Design

- The RECONNECT studies comprise 2 identical, randomized, phase 3, placebo-controlled, multicenter trials (NCT02333071 [Study 301] and NCT02338960 [Study 302]) of BMT 1.75 mg administered subcutaneously (SC) via an autoinjector pen, as desired, for the treatment of HSDD in premenopausal women
- The Core Phase of the trials included a 4-week no-drug screening/qualification period, a 4-week single-blind placebo treatment period, and a 24-week double-blind treatment period (Figure 1)

Figure 1. Study Design



BMT, bremelanotide; OLE, Open-Label Extension.
During the Screening Month, HSDD diagnosis was confirmed. The Placebo Self-Dosing Month allowed establishment of the placebo effect. After this, patients received either BMT or placebo during the randomized, double-blind Core Study Phase. Participants who completed the Core Study Phase and remained eligible were given the option to continue in the OLE Study Phase and receive BMT 1.75 mg SC on an as-desired basis.
Participants self-administered BMT 1.75 mg or placebo SC using an autoinjector pen, as desired. It was suggested that the subjects administer the study drug approximately 45 minutes prior to anticipated sexual activity.

Study Participants and Key Entry Criteria

- Healthy, premenopausal (as defined by Stages of Reproductive Aging Workshop [STRAW] criteria), nonpregnant women, ≥18 years of age, currently in a stable (≥6 months) relationship
- Diagnosed with HSDD (with or without decreased arousal) for ≥6 months
- Experienced "normal" sexual function in the past for ≥2 years
- Willing to engage in sexual activities ≥1x/month during the study
- Had *all* of the following at screening:
  - Patient Health Questionnaire-9[9] (a screening instrument for depression) total score <10 and score of 0 on Question 9
  - Female Sexual Function Index (FSFI)[10]* 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)[11,12†] total score >18
- The presence of any female sexual dysfunction other than acquired HSDD with or without decreased arousal was cause for exclusion
- Patients who dropped out of the study, were lost to follow-up, or had already received drug in the Open-Label Extension Phase were not able to participate in the exit survey

*The FSFI is a validated 19-item measure of female sexual function consisting of 6 domains: desire, arousal, lubrication, orgasm, satisfaction, and pain.[10]
†The FSDS-DAO is a 15-item instrument based on the validated 13-item Female Sexual Distress Scale-Revised (FSDS-R); both are used to evaluate aspects of sexual-related distress over the past 30 days.[11-13]

Quantitative Exit Survey

- A mixed-methods approach, including a quantitative exit survey and qualitative exit interviews, was taken to explore in-depth patients' experiences while taking BMT
- Upon completion of the 24-week double-blind study period, up to 250 participants were recruited to complete the quantitative exit survey
  - All participants gave written informed consent
  - All interested and potentially eligible patients were screened for study eligibility in person during a scheduled BMT-301/302 Visit 8 by site staff using a recruitment script
- The self-administered paper/pencil survey comprised 16 questions and was estimated to take 10 to 15 minutes to complete (Figure 2)

Figure 2. Questions Included on the Quantitative Exit Survey

Quantitative Patient Exit Survey
Part I: Treatment Experience
1. During the course of the clinical study, did you BENEFIT OVERALL from the study medication and, if so, was the benefit enough to be meaningful to you?
2. Overall, during the course of the clinical study, did you experience an increase in sexual DESIRE and, if so, was this increase enough to be meaningful to you?
3. Overall, during the course of the clinical study, did you experience an increase in SATISFYING SEXUAL EVENTS, and, if so, was this increase enough to be meaningful to you?
4. Overall, during the course of the clinical study, did you experience an increase in SEXUAL SATISFACTION, and was it meaningful to you?
5. Overall, during the course of the clinical study, did you experience an increase in feeling MENTALLY SEXUALLY AROUSED (MENTALLY SEXUALLY EXCITED), and, if so, was this increase enough to be meaningful to you?
6. Overall, during the course of the clinical study, did you experience an increase in feeling PHYSICALLY SEXUALLY AROUSED (PHYSICALLY SEXUALLY EXCITED), and, if so, was this increase enough to be meaningful to you?
7. Overall, during the course of the clinical study, did you experience an increase in your ability to have ORGASMS and, if so, was this increase enough to be meaningful to you?
8. Overall, during the course of the clinical study, did you experience an increase in how RESPONSIVE you were to your partner initiating sexual activity, and, if so, was this increase enough to be meaningful to you?
9. Overall, during the course of the clinical study, did you become less concerned about your low sexual desire, and, if so, was this decrease enough to be meaningful to you?
Part II: Overall Experience
10. Thinking about what you hoped to achieve during the clinical study, how well did the study medication meet your expectations?
11. Comparing the time before you started the study to the present time, did you experience any changes in how you felt about the following: (See Figure 5 for specific parameters).
12. Thinking about your experiences while using the study medication, how interested would you be in continuing treatment if it were available by prescription after you completed the clinical study?
13. Thinking about your overall experiences while using the study medication, how likely would you be to recommend it to a close friend who had a loss of sexual desire?
Part III: Experience With the Device
14. Considering everything about your experiences using the drug delivery device, how would you rate it overall?
15. Thinking about using the drug delivery device during the clinical study, HOW WOULD YOU RATE THE DEVICE, on the following characteristics? (See Figure 7 for specific parameters).
16. Thinking about using the drug delivery device during the clinical study, HOW IMPORTANT were the following characteristics to you? (Responses similar to Item 15, see Figure 7).

- For Questions 1 to 9, participants were asked to characterize their experience with the study drug (specific response options were tailored to each question):
  - Overall, I did not benefit
  - Overall, it was beneficial but was not meaningful to me
  - Overall, it was beneficial and was meaningful to me
- Questions 10 and 12 to 16 were scored on a 5-point scale, and Question 11 was scored on a 7-point scale (see figures for specific responses)

Qualitative Exit Interviews

- A subset of patients who participated in the 60-minute quantitative exit interview also completed an in-depth qualitative telephone interview
  - This took place after completion of all activities associated with BMT-301/302 Visit 9 (final visit) and the quantitative exit survey, but prior to initiation into the Open-Label Extension Phase with BMT
  - Data analysis consisted of analyzing qualitative data to gain insight into each patient's experience during the BMT 301/302 clinical trials; topics investigated included motivations for entering treatment, perspectives on treatment experience, reports of meaningful change, and experience with the autoinjector
  - Interviewers were blinded to treatment assignment

Statistics Applied to the Quantitative Exit Survey

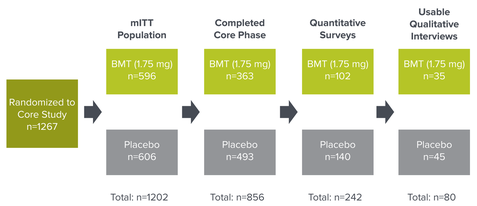
- Summary statistics (mean, standard deviation, frequency) were used to characterize subject demographics
- To evaluate differences between treatment groups (BMT vs placebo), chi-square tests were used to compare categorical variables, and *t*-tests or analysis of variance models were used to compare continuous variables

Results

Participants and Baseline Characteristics

- 1267 women were randomized in the phase 3 BMT trials (Figure 3)
  - A total of 242 participants (BMT, n=102; placebo, n=140) completed the quantitative exit survey
  - Among the subset who participated in the in-depth qualitative telephone interviews, 80 subjects had evaluable data for analysis

Figure 3. Disposition of Subjects Completing Exit Surveys



BMT, bremelanotide; mITT, modified intent-to-treat population, which was defined as all subjects in the safety population who had at least 1 double-blind follow-up visit. The safety population was defined as all subjects who were randomized and received at least 1 dose of the double-blind study medication (in the clinic or as outpatients).

- The most frequent diagnosis was HSDD with decreased arousal (Table 1), and baseline characteristics were generally similar across treatment groups
  - Participants in the BMT 1.75 group had a slightly higher body mass index (BMI) on average relative to placebo (29.6 vs 27.5)

Table 1. Baseline Characteristics (Quantitative Exit Survey Population)

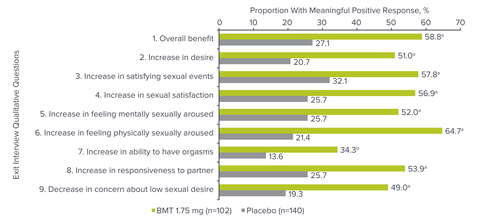
Variable	BMT 1.75 mg (n=102)	Placebo (n=140)
Mean age (SD), y	38.5 (7.2)	39.1 (6.5)
Race, n (%)		
White	91 (89.2)	122 (87.1)
Black/African American	9 (8.8)	14 (10.0)
Other	2 (2.0)	4 (2.9)
Mean BMI (SD), kg/m²	29.6 (7.5)	27.5 (5.9)
HSDD diagnosis, n (%)		
With decreased arousal	65 (63.7)	86 (61.4)
Without decreased arousal	37 (36.3)	54 (38.6)
Mean number of months since HSDD diagnosis (SD)	54.1 (45.7)	56.0 (49.9)

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

Experience With Treatment

- A meaningful overall benefit (Question 1) was noted by 58.8% of the BMT group and 27.1% of the placebo group (*P*<0.0001) (Figure 4)
- Statistically significant improvements were also seen with BMT vs placebo for other aspects of response to treatment (Figure 4)

Figure 4. Proportion of Patients With a Meaningful Response (Questions 1 to 9)

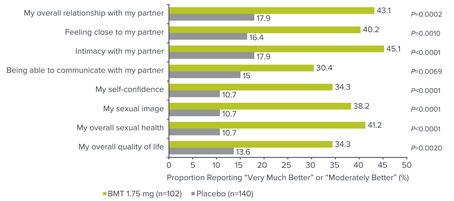


[a]*P*<0.0001 vs placebo; [b]*P*=0.0002 vs placebo.
See Figure 2 for full questions.

Overall Experience

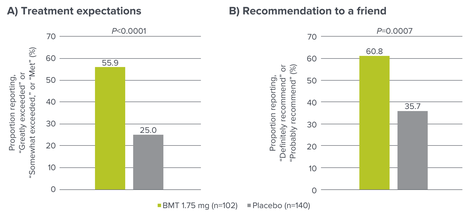
- Treatment with BMT was associated with statistically significant improvements in overall quality of life, self-confidence, overall sexual health, sexual image, and relationship with partner, compared with placebo (Figure 5)
- Treatment with BMT met or exceeded expectations in 55.9% of patients, compared with only 25% for placebo (*P*<0.0001) (Figure 6)
  - 60.8% of subjects who received BMT would recommend the treatment to a close friend who had experienced a loss of sexual desire as compared with 35.7% of those who had received placebo
- In response to Question 12, which asked participants whether they would continue treatment via prescription (if available), 57.8% of those who received BMT were "definitely interested" or "probably interested" as compared with 47.9% of those who received placebo (not statistically significant, *P*=0.2981)

Figure 5. Change in Patient Feelings and Experiences Over the Course of the Study



Question 11 was stated as: "Comparing the time before you started the study to the present time, did you experience any changes in how you felt about the following:" – with the categories listed in Figure 5. Among the choices were these responses: very much better, moderately better, a little better, about the same, a little worse, moderately worse, very much worse. *P*-values were from the chi-square tests of BMT vs placebo.

Figure 6. Impressions of Study Drug

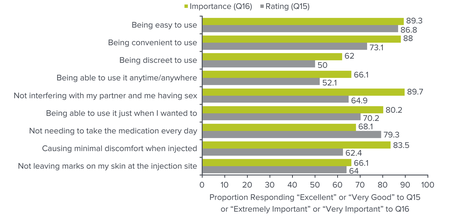


A) Question 10: "How well did the study medication (treatment) meet your expectations?" Available answers: greatly exceeded, somewhat exceeded, met my expectations, did not quite meet my expectations, did not at all meet my expectations. **B)** Question 13: "How likely would you be to recommend study medication to a close friend who had a loss of sexual desire?" Available answers: definitely recommend, probably recommend, may or may not recommend, probably not recommend, definitely not recommend. *P*-values were from the chi-square tests of BMT vs placebo.

Experience With the Device

- Overall, 62.4% of patients across both treatment groups rated the device "excellent" or "very good" (Question 14)
- There were no statistically significant differences between treatment groups for elements of Questions 15 and 16 with these exceptions (Figure 7):
  - Rating of marks left at injection site (56.9% vs 69.3% of BMT vs placebo scored as excellent or very good, *P*=0.0417)
  - Importance of not interfering with sex with partner (93.1% vs 87.1% of BMT vs placebo scored as extremely or very important, *P*=0.0417)
- Most participants assigned a positive rating (excellent or very good) to study treatment ease of use (86.8%) and not needing to take medication on a daily basis (79.3%) (Figure 7)
- Most participants regarded the following as extremely or very important: not interfering with sex with partner (89.7%), ease of use (89.3%), convenience (88%), minimal injection discomfort (83.4%), and using when desired (80.2%) (Figure 7)

Figure 7. Patient Impressions of Self-Administered Injection Device



Both questions were asked in the context of "Thinking about using the drug delivery device during the clinical study." Question 15: "How would you rate the device on the following characteristics?" Question 16: "How important were the following characteristics to you?"

Selected Verbatim Responses From Qualitative Interviews

Experience with treatment

- **Bremelanotide:** *"…I did go back to work. So, that was awkward for me because I'm sitting at work and I have all of these emotions that just – just rushed. The desire was so overwhelming that it was [laughter] for me it was new because I hadn't felt it in so long. But it was a joy for me for the same reason, I hadn't felt it in so long. But by the time – I couldn't make it to the end of the day…."*
- **Placebo:** *"I feel like it – it was very psychological and not so much physical. I was kind of hoping it would be a physical reaction, that I would just, you know, have this like overwhelming desire and I never really felt that. It was always psychological and I didn't…whether it was the medication or whether it was me psyching myself out."*

Overall experience

- **Bremelanotide:** *"Um, I would say definitely overall [it met expectations], just because, you know, it did give me that increase and that boost, uh, to – to want to that and, um, increased, you know, the sexual activity like I said from zero to two to three times a month. So, to go from not having, you know, any sex drive or even being remotely interested at all to doing that and being close with my husband, I would say it definitely, you know, um, worked for me and – and was much better. So, I think the study was worth it."*
- **Placebo:** *"Um, I would say my goals were not met, I didn't notice a change in my level of interest. Um, and I didn't notice a change in my physical response. And I was hoping that even if I wasn't interested, I at least was interested once things got started, that would have been a benefit. But I didn't notice either of those things."*

Experience with the device (regardless of treatment)

- *"I was nervous at first because I don't like needles. Um, I was hoping for a like a pill or something. But then once I actually took the drug a couple of times I realized that it doesn't hurt and it's pretty easy. So, then it was fine. You never see the needle at all."*
- *"… it was good, again it's pretty discreet, I could keep one in my purse easily. Um, so like if I – if I took it with me and didn't necessarily want to take immediately, I just, you know, kind of had it on me, that was pretty convenient."*

Conclusions

- Results from this exit survey showed that women randomized to BMT consistently reported meaningful treatment benefits compared with placebo, supporting the positive co-primary outcomes in the BMT treatment arm in the overall RECONNECT study population
- Most patients receiving BMT were interested in continuing with treatment and would recommend BMT to a close friend with HSDD
- Overall, most patients rated the self-injection device as "excellent" or "very good"
- Patients reported that the most important aspects of treatment for them were: not interfering with sex with partner, ease of use, convenience, minimal injection discomfort, and using when desired

Acknowledgments

The authors wish to thank all participants in these studies, their families, and the personnel at all study sites. The authors were responsible for all content and editorial decisions, and received no honoraria related to the development of this poster. All authors contributed to the research, writing, and reviewing of all drafts of this poster and approved the final version. These studies were sponsored by Palatin Technologies, Inc., the innovator of bremelanotide. Editorial support in the preparation of this poster was provided by Phase Five Communications, funded by AMAG Pharmaceuticals, Inc., the licensee of bremelanotide.

Disclosures

PK has been an employee of Evidera (2014-2016), which has provided consultancy services to Palatin Technologies, Inc. She has also been an employee of Procter & Gamble (1999-2009). She is currently an employee of ICON plc. DR has been a consultant and has received research support from Palatin Technologies, Inc., and AMAG Pharmaceuticals, Inc. DR, HW, and RP are employees of Evidera, which has provided consultancy services to Palatin Technologies, Inc. RJ and JL are employees of Palatin Technologies, Inc.

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E-poster presented at: 2018 Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists; Austin, Texas; April 27-30, 2018.