Safety and Efficacy of Bremelanotide for HSDD in Women: RECONNECT Study Open-Label Extension Phase Results

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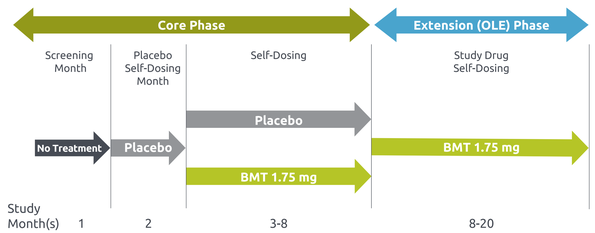
Background

- Bremelanotide (BMT), a novel cyclic 7-amino acid melanocortin-4-receptor agonist with high affinity for MC4R,[1] is an investigational drug currently in development for the treatment of hypoactive sexual desire disorder (HSDD)
- 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 (Figure 1)
- Results from the Core Study Phase have been reported previously. This presentation includes long-term safety and efficacy results from the RECONNECT Open-Label Extension (OLE) Study Phase

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.

Methods

Study Participants

- Participants had successfully completed the Core Study Phase of the studies, had no serious adverse events (SAEs) related to BMT, and met the eligibility criteria of the OLE Study Phase

Key Outcome Measures

- Safety was assessed by recording and monitoring adverse events (AEs), concomitant medication use, and clinically significant changes in physical examinations, ECGs, vital signs, and laboratory assessments
- Efficacy assessments were similar to those in the Core Study Phase, but with no hierarchy of primary and secondary endpoints (Table 1)

Table 1. Efficacy Assessments

Instrument	Measure	Items and Domains	Type of Test
FSFI[2]	Female sexual dysfunction	19 items in 6 domains, including desire, arousal, lubrication, orgasm, satisfaction, and pain; scores from 2-36	4-week recall
FSDS-DAO[3,4]	Sexual distress	15-item instrument based on the FSDS-R); scores from 0-60	Likert-like response scale; 4-week recall
FSEP-R[5,6]	Sexual encounters[a]	10-item scale used to assess sexual encounters (ie, initiation, level of desire, satisfaction with arousal, lubrication, arousal, ability to achieve orgasm, and satisfaction with the sexual encounter)	Completed within 24 hours after each sexual encounter regardless of whether study drug was used before that encounter
GAQ	Satisfaction level	4 items related to satisfaction level (ie, satisfaction with arousal, satisfaction with desire, degree of benefit while on study drug, and impact of taking study drug on relationship with partner)	Uses a 7-point numeric rating scale from 1 (very much worse) to 4 (no change) to 7 (very much better); assessed at each monthly clinic visit

FSDS-DAO, Female Sexual Distress Scale – Desire/Arousal/Orgasm; FSEP-R, Female Sexual Encounter Profile-Revised; FSFI, Female Sexual Function Index; GAQ, general assessment questionnaire.
[a]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.

Statistics

- OLE Study Phase safety and efficacy results are summarized based on descriptive analyses only, as there were no comparator arms
  - All efficacy assessments in the OLE Study Phase are exploratory
- Baseline values for event data were defined as the last 28 days in the single-blind placebo period for patients randomized to BMT (BMT-BMT group), and the last 28 days prior to the final visit of the Core Study Phase for those randomized to placebo (placebo-BMT group)
- For data collected at a single visit, baseline was defined as the last value collected during the single-blind placebo phase for those randomized to BMT, and the final visit during the Core Study Phase (ie, last visit prior to receiving BMT) for those randomized to placebo

Results

Baseline Characteristics

- 1267 women were randomized in the Core Study Phase
  - A total of 684 participants continued in the OLE Study Phase in Studies 301 and 302
  - The baseline characteristics of the initial Core Study Phase cohort were maintained in the OLE Study Phase cohort
- The majority of subjects in the studies were white (>84%)
  - Mean ages for Studies 301 and 302 were 38.7 and 39.6 years, respectively, with ages ranging from 19 to 55 years

Safety

- In Study 301, the median total number of BMT injections for the placebo-BMT and BMT-BMT groups were 12 and 27, respectively
  - In Study 302, the median total number of BMT injections for the placebo-BMT and BMT-BMT groups were 13 and 25, respectively
- The most common (≥5% of subjects) treatment-emergent AEs (TEAEs) during the OLE Study Phase were nausea, flushing, sunburn, and headache (Table 2)
- Subjects switching from placebo had a higher incidence of AEs than those continuing on BMT (82.4% vs 63.7%, respectively, in Study 301, and 74.3% and 63.1%, respectively, in Study 302)
  - This higher incidence of AEs was consistent with the overall rate of AEs for the BMT treatment groups in the Core Study Phase
- AEs were treatment-limiting in 12.1% and 6.2% of subjects in the BMT-BMT group and 25.5% and 23.6% in the placebo-BMT group in Studies 301 and 302, respectively
- The only severe TEAE experienced by >1 participant in both studies was nausea. In OLE Study Phase 301, fatigue, flushing, upper abdominal pain, endometriosis, and headache occurred as severe TEAEs in >1 participant
- Three patients (2 in the placebo-BMT group and 1 in the BMT-BMT group) experienced treatment-emergent SAEs
- One subject developed a case of acute hepatitis. At the end of the last visit on study, subject had 20x elevation of transaminases, >2x elevation in bilirubin, and scleral icterus. At 6-month follow-up, subject's AST and ALT were 2x the upper limit of normal but returned to normal again 6 months later
- No deaths occurred during the study
- Maximal, transient, and mild increases in SBP and DBP were noted approximately 2 hours post-BMT dosing and were accompanied by similarly mild decreases in pulse rates, such that there would be no expected increases in overall heart rate-BP product. These mild transient changes in BP and pulse rates were not accompanied by other clinical symptoms
- No clinically significant effects on ECG, weight, depression, or suicidal ideation, or effect of alcohol consumption were observed

Table 2. TEAEs in Open-Label Extension Phase (≥5% of Patients)[a]

	Study 301		Study 302	
Incidence, n (%)	Placebo-BMT (n=239)	BMT-BMT (n=124)	Placebo-BMT (n=191)	BMT-BMT (n=130)
Nausea	108 (45.2)	46 (37.1)	84 (44.0)	37 (28.5)
Flushing	64 (26.8)	24 (19.4)	41 (21.5)	11 (8.5)
Sunburn	30 (12.6)	12 (9.7)	19 (9.9)	22 (16.9)
Headache	30 (12.6)	13 (10.5)	29 (15.2)	9 (6.9)
Upper respiratory tract infection	13 (5.4)	11 (8.9)	6 (3.1)	5 (3.8)
Injection site pain	12 (5.0)	3 (2.4)	3 (1.6)	7 (2.2)
Fatigue	17 (7.1)	4 (3.2)	5 (2.6)	3 (2.3)
Vomiting	15 (6.3)	3 (2.4)	9 (4.7)	3 (2.3)
Injection site reaction	14 (5.9)	2 (1.6)	5 (2.6)	4 (3.1)
Urinary tract infection	5 (2.1)	9 (7.3)	10 (5.2)	4 (3.1)

BMT, bremelanotide; OLE, Open-Label Extension; TEAE, treatment emergent adverse event.
[a]TEAEs in OLE Study Phase, independent of events reported in Core Study Phase.

Efficacy

- In the randomized, placebo-controlled Core Study Phase, both studies met the prespecified co-primary endpoints with a statistically significant increase in desire (FSFI-D) and a decrease in distress (FSDS-DAO Item 13) for participants treated with BMT versus those treated with placebo[7]

FSFI-D and FSDS-DAO: Item 13

- BMT was associated with a sustained improvement in FSFI-D and a sustained reduction in FSDS-DAO Item 13 score throughout the 52-week OLE Study Phase, indicating an increase in desire and a decrease in distress, respectively (Figure 2)
  - For the placebo-BMT group, these changes were similar to the changes observed for the BMT group during the Core Study

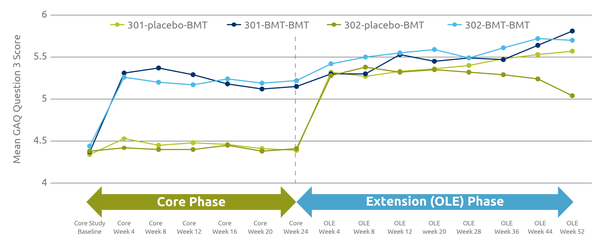
Additional Efficacy Endpoints

- There was a sustained improvement in FSFI total score, FSDS-DAO arousal and total scores, and FSEP-R scores for satisfaction with desire and arousal
- There was no consistent change in the number of SSEs associated with the study drug in either study during the 52-week OLE Study Phase
  - However, there was an observed improvement in the percentage of sexual encounters that were considered satisfying in both studies
- According to the responses to GAQ Question 3, participants felt that they had significantly benefited from treatment compared with those taking placebo (Figure 3)

Figure 2. FSFI-D and FSDS-DAO Item 13[a] Scores Throughout RECONNECT Studies (OLE Study Population)

BMT, bremelanotide; FSDS-DAO, Female Sexual Distress Scale – Desire/Arousal/Orgasm; FSFI-D, Female Sexual Function Index – desire domain; OLE, Open-Label Extension.
[a]For Figure 2A: Questions 1 and 2 of the FSFI comprise the desire domain. Q1: "Over the past 4 weeks, how often did you feel sexual desire or interest?" Possible answers: almost always or always, most times (more than half the time), sometimes (about half the time), a few times (less than half the time), or almost never or never. Q2: "Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest?" Possible answers: very high, high, moderate, low, very low, or none at all. Scores for both answers range from 5 to 1 in order given. For Figure 2B: FSDS-DAO 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.

Figure 3. GAQ Question 3 Scores



BMT, bremelanotide; DB, double-blind; GAQ, general assessment questionnaire; OLE, Open-Label Extension.
Question 3 asks: "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?" A score ≥5 indicates benefit.

Conclusions

- BMT, an investigational, self-administered, as-desired, SC injection, was generally well tolerated; most TEAEs were mild or moderate in maximum severity and transient, with resolution shortly after treatment administration
  - There were no new safety patterns or findings in subjects who received BMT throughout the entire study (Core Study and OLE Study Phases) for a treatment period of up to 76 weeks
- The results from the OLE Study Phase provided additional support for the potential use of BMT as an effective treatment of HSDD in premenopausal women
  - Treatment benefits were maintained for participants who had received BMT during the Core Study Phase (BMT-BMT)
  - Similar rapid onset of treatment benefits were observed for participants who had received placebo during the Core Study Phase (placebo-BMT)
- Based on the totality of data from this OLE Study Phase, BMT exposure over a 52-week treatment period demonstrated an acceptable safety profile and treatment benefits that support extended use in premenopausal women with HSDD

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Disclosures

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