Bremelanotide for Hypoactive Sexual Desire Disorder: Age and Weight Subgroup Efficacy Analyses From the RECONNECT Studies

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Background

- The most common sexual concern expressed by women with female sexual dysfunction is diminished or lack of desire for sexual activity.[1] When accompanied by distress, this may be diagnosed as hypoactive sexual desire disorder (HSDD)[2,3]
- Bremelanotide (BMT), a novel cyclic 7-amino acid melanocortin-4-receptor (MC4R) agonist with high affinity for MC4R, is an investigational drug currently in development for the treatment of HSDD[4]
  - BMT is taken as desired to improve sexual desire accompanied by a decrease in personal distress in premenopausal women diagnosed with HSDD
- Analyses of the co-primary and key secondary endpoints were performed as exploratory analyses for the age and weight subgroups of the RECONNECT studies to assess the consistency of BMT's effect

Methods

- The RECONNECT studies were 2 identical, multicenter, randomized, placebo-controlled, phase 3 trials
  - Eligible participants included healthy, premenopausal (based on Stages of Reproductive Aging Workshop [STRAW] criteria), nonpregnant women, ≥18 years of age, currently in a stable (≥6 months) relationship, who were diagnosed with HSDD for ≥6 months (with or without decreased arousal)
  - Participants had experienced "normal" sexual function at some time in the past for ≥2 years and were willing to engage in sexual activities ≥1×/month during the study
  - A 4-week, single-blind, placebo run-in period was followed by a 24-week, double-blind treatment period in which participants self-administered BMT 1.75 mg or placebo subcutaneously via autoinjector pen, as desired, prior to sexual activity
  - The co-primary efficacy endpoints were change from baseline to end of study in Female Sexual Function Index desire domain (FSFI-D) and Female Sexual Distress Scale – Desire/Arousal/Orgasm (FSDS-DAO) distress resulting from low desire (Item 13)
    - FSFI is a validated 19-item measure of female sexual function consisting of 6 domains: desire, arousal, lubrication, orgasm, satisfaction, and pain[5,6]
      - Total score (sum of the domain scores) ranges from 2 to 36
      - Desire domain consists of 2 questions
      - Recall period is the past 4 weeks
      - Higher scores indicate a greater level of sexual function
    - FSDS-DAO is a validated 15-item instrument based on the 13-item Female Sexual Distress Scale–Revised; both are used to evaluate aspects of sexual-related distress over the past 30 days[7,8]
      - Item 13 relates specifically to "bother" related to sexual desire
      - Higher scores indicate greater sexual-related distress
  - Key secondary endpoint was change from baseline to end of study in the number of sexually satisfying event (SSE) items from Female Sexual Encounter Profile–Revised
- Modified intent-to-treat (mITT) population (the primary efficacy population) included all randomized participants who used ≥1 dose of study drug and had ≥1 double-blind follow-up visit
- For the current exploratory analyses, participants from the 2 trials were separated into age and weight quartiles

Results

Participants and Baseline Characteristics

- Of 1267 participants randomized in the 2 trials, 1202 were included in the mITT population (606 placebo; 596 BMT)
- The age range was 19 to 56 years; the weight range was 39.8 to 189.9 kg (Table 1)

Table 1. Baseline Characteristics for the Phase 3 Integrated RECONNECT Studies (mITT Population)

Variable	Integrated Studies 301 and 302		
	Placebo (n=606)	BMT (n=596)	Total (N=1202)
Age, years			
Mean (SD)	38.8 (7.06)	38.5 (7.03)	38.7 (7.05)
Minimum	19	20	19
First quartile	34.0	33.0	34.0
Median	39.0	39.0	39.0
Third quartile	44.0	44.0	44.0
Maximum	55	56	56
Weight, kg			
Mean (SD)	76.81 (18.939)	78.59 (20.074)	77.69 (19.522)
Minimum	39.8	46.4	39.8
First quartile	62.90	63.30	63.10
Median	73.45	74.70	74.00
Third quartile	86.60	89.50	87.70
Maximum	179.2	189.9	189.9
Diagnosis, n (%)			
HSDD with decreased arousal	434 (71.6)	420 (70.5)	854 (71.0)
HSDD without decreased arousal	172 (28.4)	176 (29.5)	348 (29.0)
Months since HSDD diagnosis, mean (SD)	47.9 (44.04)	46.6 (42.13)	47.2 (43.09)

BMT, bremelanotide; HSDD, hypoactive sexual desire disorder; mITT, modified intent-to-treat; SD, standard deviation.

Efficacy: Integrated RECONNECT Population

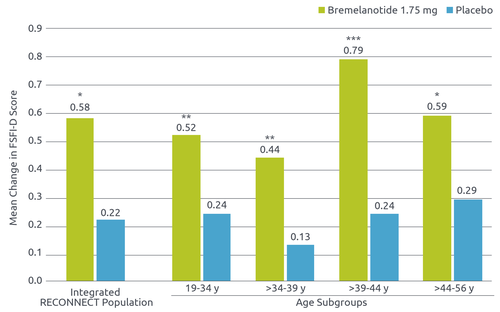
- For the total integrated RECONNECT population
  - The difference in mean changes from baseline (BMT minus placebo) was 0.36 for FSFI-D (Figures 1A and 2A) and -0.3 for FSDS-DAO Item 13 (Figures 1B and 2B)
  - Mean changes from baseline in the number of SSEs associated with study drug and reported within 72 hours did not significantly differ between treatment arms

Efficacy: Age Subgroups

- Differences in mean FSFI-D and FSDS-DAO Item 13 changes from baseline were statistically significant ($P<0.05$) for each age quartile (Figure 1)
- Mean changes from baseline in the number of SSEs associated with study drug and reported within 72 hours did not significantly differ between treatment arms for any age quartile

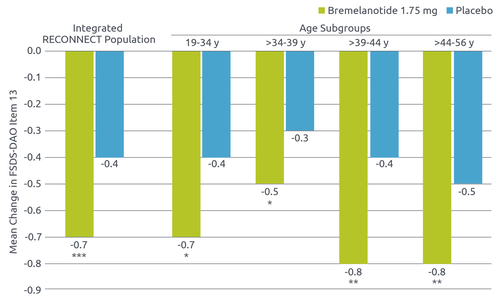
Figure 1. Mean Change in FSFI-D and FSDS-DAO Item 13 From Baseline to End of Study in the Integrated Phase 3 RECONNECT Studies: Age Subgroups (mITT Population)

A. FSFI-D



FSFI-D	Integrated RECONNECT	Age Subgroup			
		19-34 y	>34-39 y	>39-44 y	>44-56 y
BMT, n	595	175	139	142	139
Placebo, n	603	156	150	153	144
Difference in mean Δ	0.36	0.28	0.31	0.55	0.3

B. FSDS-DAO Item 13



FSDS-DAO Item 13	Integrated RECONNECT	Age Subgroup			
		19-34 y	>34-39 y	>39-44 y	>44-56 y
BMT, n	595	175	139	142	139
Placebo, n	599	156	149	152	142
Difference in mean Δ	-0.3	-0.3	-0.2	-0.4	-0.3

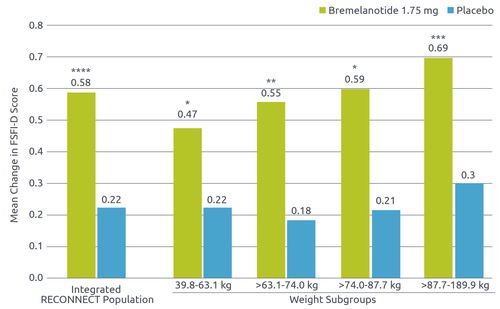
BMT, bremelanotide; FSFI-D, Female Sexual Function Index desire domain; FSDS-DAO, Female Sexual Distress Scale – Desire/Arousal/Orgasm; mITT, modified intent-to-treat.
*$P<0.05$ vs placebo.
**$P<0.01$ vs placebo.
***$P<0.0001$ vs placebo.

Efficacy: Weight Subgroups

- Differences in mean FSFI-D and FSDS-DAO Item 13 changes from baseline were statistically significant ($P<0.05$) for each weight quartile except for mean change in Item 13 from baseline for women 39.8-63.1 kg (Figure 2)
- Mean changes from baseline in the number of SSEs associated with study drug and reported within 72 hours did not significantly differ between treatment arms for any weight quartile

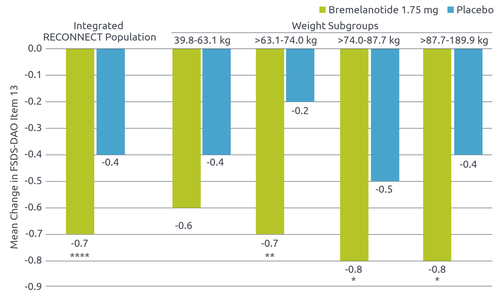
Figure 2. Mean Change in FSFI-D and FSDS-DAO Item 13 From Baseline to End of Study in the Integrated Phase 3 RECONNECT Studies: Weight Subgroups (mITT Population)

A. FSFI-D



FSFI-D	Integrated RECONNECT	Weight Subgroup			
		39.8-63.1 kg	>63.1-74.0 kg	>74.0-87.7 kg	>87.7-189.9 kg
BMT, n	595	146	143	146	159
Placebo, n	603	156	154	153	140
Difference in mean Δ	0.36	0.25	0.37	0.38	0.39

B. FSDS-DAO Item 13



FSDS-DAO Item 13	Integrated RECONNECT	Weight Subgroup			
		39.8-63.1 kg	>63.1-74.0 kg	>74.0-87.7 kg	>87.7-189.9 kg
BMT, n	595	146	143	146	159
Placebo, n	599	155	154	151	139
Difference in mean Δ	-0.3	-0.2	-0.5	-0.3	-0.4

BMT, bremelanotide; FSFI-D, Female Sexual Function Index desire domain; FSDS-DAO, Female Sexual Distress Scale – Desire/Arousal/Orgasm; mITT, modified intent-to-treat.
*$P<0.05$ vs placebo.
**$P<0.01$ vs placebo.
***$P<0.001$ vs placebo.
****$P<0.0001$ vs placebo.

Safety

- In the integrated core studies, the safety profile of BMT was consistent with prior clinical experience. The most frequent adverse events were mild/moderate nausea (any incidence of nausea: 40% in the BMT treatment group vs 1% in the placebo group), flushing (20% vs <1%), and headache (11% vs 2%)

Conclusions

- The investigational MC4R agonist bremelanotide, which was self-administered as desired (SC via an autoinjector pen), demonstrated efficacy for up to 6 months in premenopausal women with HSDD regardless of age
- Bremelanotide significantly improved desire across weight quartiles and showed a trend in decreasing distress
- The results of these subgroup analyses were consistent with the overall safety and efficacy results from the phase 3 RECONNECT studies
  - These exploratory analyses support previously reported results, further demonstrating that bremelanotide is a potentially efficacious treatment for HSDD in premenopausal women

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Disclosures

JS has served on advisory boards or has been a consultant for AbbVie, Allergan, AMAG, Amgen, Ascend Therapeutics, Azure Biotech, Bayer, CEEK Enterprises, Millendo, Mitsubishi Tanabe Pharma, ObsEva, Radius Health, Sanofi, Sebela, Sermonix, Shionogi, Lupin/Symbiotec, TherapeuticsMD, and Valeant. He has also served on the speaker's bureau for Duchesnay, Novo Nordisk, Shionogi, and Valeant. He has received grants/research funding from AbbVie, Allergan, Agile Therapeutics, Bayer, Myovant Sciences, New England Research Institute, ObsEva, Palatin Technologies, Symbio Research, and TherapeuticsMD. He owns stock in Sermonix. SK has served on advisory boards or has been a consultant for AMAG, Duchesnay, Emotional Brain, Valeant, Endoceutics, Ivix, Palatin Technologies, Pfizer, Shionogi, Materna, Nuelle, TherapeuticsMD, SST, and Lupin/Symbiomix. She has stock options in Vieve. AC has served on advisory boards or has been a consultant for Alkermes, AMAG, Fabre Kramer, Ivix, Palatin Technologies, S1 Biopharma, Sprout, Takeda, and Valeant. She has received grants from Axsome, Endoceutics, Janssen, Palatin Technologies, Sage, and Takeda. She has shares or restricted stock units in Euthymics and S1 Biopharma. RJ and JL are employees of Palatin Technologies (sponsor of the trial).

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