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Reliability and Validity of the Female Sexual Distress Scale–Desire/Arousal/Orgasm Instrument in a Phase 2B Dose-Ranging Study of Bremelanotide

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Accepted Abstract

Introduction: Bremelanotide (BMT) is a novel melanocortin-receptor-4 agonist currently in clinical development for the treatment of female sexual dysfunction (FSD). We evaluated the reliability and validity of the Female Sexual Distress Scale-Desire/Arousal/Orgasm (FSDS-DAO) as an instrument to assess the efficacy of BMT in women with FSDs.

Hypothesis: FSDS-DAO is a valid instrument to assess therapeutic response in women with FSD.

Methods: After screening, premenopausal women with hypoactive sexual desire disorder and/or female sexual arousal disorder received an in-clinic subcutaneous (SC) placebo dose followed by 4 weeks of SC placebo self-dosing (baseline). Subjects were then randomized to double-blind placebo or BMT 0.75, 1.25, or 1.75 mg for 12 weeks of at-home self-dosing. An exploratory efficacy measure was the change from baseline to end of study (EOS) in the FSDS-DAO. Cronbach's alpha and Spearman's correlation were calculated to assess internal consistency reliability and test-retest reliability, respectively. Construct validity was evaluated by examining the correlation of the FSDS-DAO total score with the Female Sexual Encounter Profile-Revised, Female Sexual Function Index (FSFI) subscales and total score, Global Assessment Question (GAQ) item scores, and number of sexually satisfying events (SSEs) at baseline and EOS using Spearman's rank correlation coefficients. The ability of FSDS-DAO scores to discriminate according to disease severity was assessed using general linear models with Scheffe's post hoc comparisons.

Results: Mean change from baseline to EOS in FSDS-DAO total score was greater with BMT 1.75 mg (–13.1; P=0.0133) and 1.25/1.75 mg pooled (–11.1; P=0.0360) compared with placebo (–6.8). Cronbach's alpha was >0.9 at each visit. Spearman's correlation between the FSDS-DAO scores at screening and after placebo was 0.62 (P<0.001), indicating acceptable test-retest reliability. All correlations of the FSDS-DAO total score with previously validated questionnaires were statistically significant at baseline and EOS. Mean FSDS-DAO total score was significantly higher in women reporting <2 vs ≥2 SSEs at EOS (29.4 vs 17.9, respectively; P<0.001). Severity of sexual dysfunction, assessed by the FSFI subscales and total score, was linearly correlated with FSDS-DAO total score at baseline and EOS. The FSDS-DAO discriminated at baseline and EOS between scores reflecting worsening (1–3), no change (4), and improvement (5–7) on GAQ items related to satisfaction with arousal (GAQ #1) and desire (GAQ #2) and patient's self-assessment of benefit (GAQ #3).

Conclusions: The FSDS-DAO demonstrates internal consistency and test-retest reliability, and construct and discriminant validity. Thus, the FSDS-DAO is a reliable and valid measure to assess sexual-related distress in women with FSDs.

Discussion: The addition of questions regarding arousal and orgasm to the original FSDS-R retains the reliability and validity of the measure.

Introduction

The Female Sexual Distress Scale–Desire/Arousal/Orgasm (FSDS-DAO) is a 15-item questionnaire designed to evaluate multiple aspects of sexual distress. It modifies the Female Sexual Distress Scale–Revised (FSDS-R)[1] by having two additional items, one on arousal ("How often did you feel concerned by difficulties with sexual arousal?"), the other on orgasm ("How often did you feel frustrated by problems with orgasm?"). Published evidence[1] supports the test-retest reliability and construct validity of the FSDS-R in women with hypoactive sexual desire disorder (HSDD[2]). For the FSDS-DAO, however, no psychometric evaluation has yet been reported.

Bremelanotide (BMT) is a novel melanocortin-receptor-4 agonist[3,4] currently in clinical development for the treatment of acquired female sexual dysfunctions (FSD).[5,6] Completed studies include a phase 2B clinical trial of subcutaneous BMT self-dosing on an at-home, as-needed basis by premenopausal women with FSD. The study's outcome measures included the Female Sexual Function Index (FSFI), the Women's Inventory of Treatment Satisfaction (WITS-9), a Global Assessment Questionnaire (GAQ), the numbers of reported sexually satisfying events (SSEs), and the FSDS-DAO. Using these data, we evaluated the reliability and validity of the FSDS-DAO.

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Hypothesis

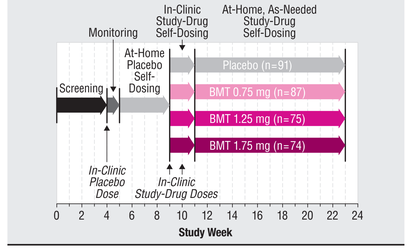
The FSDS-DAO is a valid instrument to assess therapeutic response in women with FSD.

Methods

Study Subjects. All subjects were premenopausal women with a ≥6-month duration of HSDD and/or female sexual arousal disorder (FSAD[2]), diagnosed by a qualified clinician using validated instruments and a diagnostic interview. Each subject was in a stable relationship and was willing to be sexually active at least once per month.

Study Design. After a 4-week, no-treatment screening period to confirm their FSD diagnosis, all subjects received a single-blind, in-clinic subcutaneous placebo dose, followed by 4 weeks of single-blind, at-home placebo self-dosing (baseline period). Subjects were then randomized to double-blind placebo or BMT 0.75, 1.25, or 1.75 mg, administered as two in-clinic study-drug self-dosings spaced a week apart, followed, a week later, by 12 weeks of at-home, as-needed self-dosing (by pre-filled syringe) ~45 minutes prior to anticipated sexual activity (not exceeding 1 dose per day or 16 doses during a 4-week period). The study design is schematized in Figure 1.

Figure 1. Study Design



Note: At-home placebo self-dosing period=baseline.
BMT, bremelanotide.

FSDS-DAO Data. Subjects completed the FSDS-DAO at time points including the start of screening (Visit 1), the end of screening (Visit 2, at the end of Week 4), the end of baseline placebo self-dosing (Visit 5, at the end of Week 9), and the end of 12 weeks of at-home study-drug use (Visit 12, at the end of Week 23). In the FSDS-DAO, all responses are on a Likert-type scale ranging from 0 ("never") to 4 ("always"), pertaining to a 30-day recall period. The total score is the sum of responses, and ranges from 0 to 60; a higher score indicates greater sexual distress.

FSDS-DAO Reliability/Validity Analyses. To evaluate the FSDS-DAO's internal consistency, Cronbach's alpha was calculated for the total scores at Visits 1, 2, 5, and 12. To evaluate the instrument's test-retest reliability, a Spearman's correlation coefficient was calculated for total scores between Visits 1 and 2.

Construct validity was assessed using data from Visits 5 and 12. For this purpose, Spearman's rank correlation coefficients were utilized to examine the correlation of FSDS-DAO total score with FSFI total score, with FSFI subscale scores (for desire, arousal, lubrication, orgasm, satisfaction, and pain), with WITS-9 total score, with GAQ item scores (for satisfaction with arousal, satisfaction with desire, and benefit from study drug), and with the number of SSEs per month (defined by responses of "yes" to Question 10 of the Female Sexual Encounter Profile–Revised).

Discriminant validity (the ability of FSDS-DAO total scores to discriminate according to disease severity defined by other measures) was assessed using data from Visits 5 and 12. For this purpose, Scheffe's test (adjusted for multiple comparisons) was applied to stratified findings for FSFI total score, FSFI subscale scores (for desire, arousal, and satisfaction), GAQ item scores (for satisfaction with arousal and with desire), and, for Visit 12, the number of SSEs per month.

Results

Subject Disposition. Of 1,142 screened subjects, 397 were randomized and 327 completed 1 month of double-blind study-drug use at home, thereby composing the study's modified intent-to-treat (mITT) population. Analyses of FSDS-DAO validity and reliability were based on the evaluable mITT population, consisting of all subjects with an FSDS-DAO total score at Visit 1 and at one or more follow-up visits. The sample comprised 325 subjects at Visit 1, 318 at Visit 2, 323 at Visit 5, and 309 at Visit 12.

Subject Characteristics. The baseline characteristics of all double-blind study-drug recipients (the study's safety population) are summarized in Table 1. Overall, 74% had mixed HSDD/FSAD, 23% had solely HSDD, and 3% had solely FSAD. Of the 74% with a mixed diagnosis, 85% had HSDD as their primary diagnosis. Overall, most subjects had regular periods (79%) and were not using oral contraceptives (87%).

Table 1. Subjects' Baseline Characteristics (Safety Population)

		BMT Groups			
Characteristic	Placebo Group (N=97)	0.75 mg (N=100)	1.25 mg (N=99)	1.75 mg (N=98)	1.25/ 1.75 mg Pooled (N=197)
Age (years), mean (SD)	37.0 (7.7)	37.6 (7.8)	35.7 (7.2)	37.0 (7.6)	36.4 (7.4)
Race, n (%)					
White	75 (77)	71 (71)	65 (66)	70 (71)	135 (69)
Black	19 (20)	25 (25)	32 (32)	23 (23)	55 (28)
Other	3 (3)	4 (4)	2 (2)	5 (5)	7 (4)
Weight at screening (lbs), mean (SD)	164.4 (42.1)	168.2 (37.9)	174.0 (43.2)	179.2 (45.9)[a]	176.5 (44.5)[b]
BMI at screening (kg/m^2), mean (SD)	27.7 (6.2)	28.5 (6.6)	29.2 (7.1)	29.9 (7.2)[a]	29.5 (7.1)[b]
FSD diagnosis, n (%)					
HSDD	24 (25)	20 (20)	24 (24)	24 (24)	48 (24)
FSAD	4 (4)	3 (3)	3 (3)	2 (2)	5 (3)
Mixed	69 (71)	77 (77)	72 (73)	72 (73)	144 (73)
Menses frequency regular, n (%)	72 (74)	75 (75)	86 (87)	79 (81)	165 (84)
Used oral contraception within the 30 days before screening, n (%)	12 (12)	15 (15)	11 (11)	15 (15)	26 (13)

[a]N=97. [b]N=196.
BMI, body mass index; BMT, bremelanotide; FSAD, female sexual arousal disorder; FSD, female sexual dysfunctions; HSDD, hypoactive sexual desire disorder; SD, standard deviation.

FSDS-DAO Total Score. In the mITT population, mean baseline values of FSDS-DAO total score ranged from 30.5 to 33.3, depending on treatment group. From baseline to end of study, the mean (SD) change in total score was –6.8 (13.6) for placebo, versus –7.4 (13.5) for BMT 0.75 mg, –9.2 (10.8) for BMT 1.25 mg, –13.1 (12.9) for BMT 1.75 mg, and –11.1 (12.0) for BMT 1.25/1.75 mg pooled. By Van Elteren test, the differences from placebo attained statistical significance (p<0.05) at 1.75 mg (p=0.0133) and 1.25/1.75 mg pooled (p=0.0360).

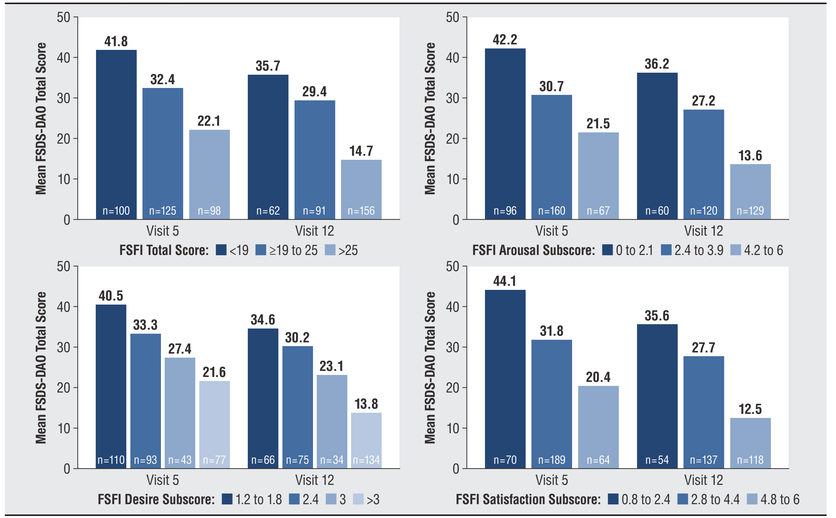
Internal Consistency. At each of the visits for which it was calculated, Cronbach's alpha for the FSDS-DAO was >0.90 (Table 2).

Table 2. Internal Consistency of the FSDS-DAO (Evaluable mITT Population)

	Visit			
Variable	1	2	5	12
N	325	318	323	309
Cronbach's alpha	0.912	0.936	0.961	0.972

FSDS-DAO, Female Sexual Distress Scale–Desire/Arousal/Orgasm; mITT, modified intent-to-treat.

Figure 2. Discriminant Validity of FSDS-DAO Total Score, by Stratified FSFI Total Scores and Stratified FSFI Subscale Scores (Evaluable mITT Population)



FSDS-DAO, Female Sexual Distress Scale–Desire/Arousal/Orgasm; FSFI, Female Sexual Function Index; mITT, modified intent-to-treat.

Test-Retest Reliability. At Visits 1 and 2, the mean (SD) FSDS-DAO total score among 318 subjects was 39.3 (9.3) and 40.1 (10.3), respectively. For total scores at these visits, the Spearman's correlation coefficient was 0.62 (p<0.001).

Construct Validity. At Visits 5 and 12, all correlations between FSDS-DAO total score and other FSD measures were statistically significant (Table 3). For FSFI total score; the FSFI desire, arousal, lubrication, orgasm, and satisfaction subscores; WITS-9 total score; and GAQ items, the correlations ranged from r=–0.41 to r=–0.67. For number of SSEs, it was –0.32 at Visit 12. Except for number of SSEs, all correlations were larger at Visit 12 than at Visit 5.

Table 3. Correlations[a] Between FSDS-DAO Total Score and Other FSD Measures (Evaluable mITT Population)

	Visit 5 (N=323)		Visit 12 (N=309)	
Comparator	r	p Value	r	p Value
FSFI total score	–0.65	<0.0001	–0.66	<0.0001
Desire subscore	–0.58	<0.0001	–0.63	<0.0001
Arousal subscore	–0.59	<0.0001	–0.64	<0.0001
Lubrication subscore	–0.44	<0.0001	–0.41	<0.0001
Orgasm subscore	–0.43	<0.0001	–0.55	<0.0001
Satisfaction subscore	–0.67	<0.0001	–0.66	<0.0001
Pain subscore	–0.17	0.0021	–0.21	0.0001
WITS-9 total score	–0.55	<0.0001	–0.64	<0.0001
GAQ item 1 (satisfaction with arousal)	–0.46	<0.0001	–0.57	<0.0001
GAQ item 2 (satisfaction with desire)	–0.45	<0.0001	–0.56	<0.0001
GAQ item 3 (benefit from study drug)	–0.41	<0.0001	–0.54	<0.0001
Number of SSEs per month[b]	–0.42	<0.0001	–0.32	<0.0001

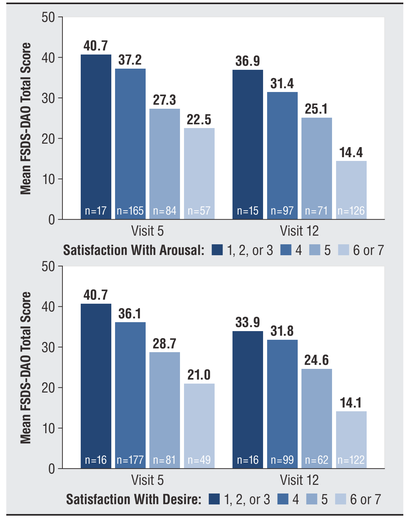
[a]Spearman's rank correlation coefficients. [b]N=314 at Visit 5, 267 at Visit 12.
FSD, female sexual dysfunctions; FSDS-DAO, Female Sexual Distress Scale–Desire/Arousal/Orgasm; FSFI, Female Sexual Function Index; GAQ, Global Assessment Questionnaire; mITT, modified intent-to-treat; SSEs, sexually satisfying events; WITS-9, Women's Inventory of Treatment Satisfaction.

Discriminant Validity, by FSFI Scores. At Visits 5 and 12, subjects' FSDS-DAO total scores varied significantly by subjects' severity of sexual dysfunction, as assessed by FSFI total score and by FSFI subscale scores for desire, arousal, and satisfaction (Figure 2). By Scheffe's test, the ability of the FSDS-DAO total score to discriminate between FSFI levels was statistically significant (p<0.05) except for discrimination at Visit 12 between the two worst FSFI desire-subscale score levels.

Discriminant Validity, by GAQ Scores. At Visits 5 and 12, subjects' FSDS-DAO total scores varied significantly by subjects' self-ratings of satisfaction with arousal and with desire, as assessed by GAQ items (Figure 3). By Scheffe's tests, the ability of the FSDS-DAO total score to discriminate between GAQ satisfaction levels was statistically significant except for discriminations between worsening (1, 2, or 3) and no change (4). Also, FSDS-DAO total score failed to discriminate at Visit 12 between worsening and the lowest level of improved satisfaction with desire (1–3 versus 5). However, all GAQ subgroups with scores of 1, 2, or 3 had ≤17 subjects. At Visit 5, FSDS-DAO total score failed to discriminate between levels of improved satisfaction with arousal (5 versus 6–7). However, Visit 5 marked the end of baseline placebo self-dosing.

Discriminant Validity, by Number of SSEs. At Visit 12, mean (SD) FSDS-DAO total score was significantly higher (worse) among the 119 women reporting <2 SSEs per month than among the 148 women reporting ≥2 SSEs, at 29.4 (13.6) versus 17.9 (12.8) (p<0.001, Scheffe's test).

Figure 3. Discriminant Validity of FSDS-DAO Total Score, by Stratified GAQ Item Scores (Evaluable mITT Population)



FSDS-DAO, Female Sexual Distress Scale–Desire/Arousal/Orgasm; GAQ, Global Assessment Questionnaire; mITT, modified intent-to-treat.

Conclusions

The FSDS-DAO demonstrates internal consistency, test-retest reliability, and construct and discriminant validity. The FSDS-DAO is a reliable and valid measure to assess sexual distress in women with FSD.

Discussion

The addition of questions regarding arousal and orgasm maintains the reliability and validity of the FSDS-DAO's precursor, the FSDS-R. FSDS-DAO total score correlated highly with previously validated FSD measures at the beginning (Visit 5) and end (Visit 12) of the double-blind dosing period.

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