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Responder Analyses from a Phase 2b Dose-Ranging Study of Bremelanotide

Stanley Althof, PhD,[1] Leonard R. Derogatis, PhD,[2] Sally Greenberg, PhD,[3] Anita H. Clayton, MD,[4] Robert Jordan,[5] Johna Lucas, MD,[5] and Carl Spana, PhD[5]

ABSTRACT

Background: Responder analyses are used to determine whether changes that occur during a clinical trial are clinically meaningful; for subjective endpoints such as those based on patient-reported outcomes (PROs), responder analyses are particularly useful.

Aim: To identify the minimal clinically important difference (MCID) for selected scores on questionnaires assessing female sexual functioning and to use these differences to analyze the response in a large, controlled, phase 2b, dose-finding study of bremelanotide in premenopausal women with hypoactive sexual desire disorder (HSDD) and mixed HSDD/female sexual arousal disorder (FSAD).

Methods: The responder analyses were performed for the change from baseline to end of study for a total of 7 endpoints. Each PRO endpoint was assessed using at least 1 of 4 types of responder analyses: a planned analysis anchored to MCIDs based on expert estimates (historical anchors); post hoc analyses based on self-reported global benefit; receiver operating characteristic (ROC) curves; and cumulative distribution function. The pre-specified analysis groups were all female sexual dysfunction (FSD)-based diagnoses (all study participants), those with HSDD alone, and a combined group of those with FSAD alone plus those with mixed HSDD/FSAD. Post hoc analyses were also performed for subjects with mixed HSDD/FSAD with a primary diagnosis of HSDD.

Outcomes: MCIDs based on the ROC curves for changes in Female Sexual Function Index—desire domain, Female Sexual Distress Scale—Desire/Arousal/Orgasm (FSDS-DAO) total score, FSDS-DAO item 13 and 14 scores, and number of satisfying sexual events.

Results: Outcomes matched those based on input from clinical experts. For all 7 endpoints, responder rates at the 1.75 mg dose in the overall modified intention-to-treat population achieved statistical significance compared with placebo ($P \leq .03$).

Clinical Implications: These responder definitions were subsequently used in the bremelanotide phase 3 registration studies (RECONNECT) that evaluated the safety and efficacy of the bremelanotide 1.75 mg subcutaneous dose in premenopausal women with HSDD.

Strengths & Limitations: MCIDs for this study were based on changes from a single-blind phase to account for changes due to the placebo effect. These analyses were restricted to a study population composed only of premenopausal women with a clinical diagnosis of HSDD and/or FSAD and were based on data from the same clinical trial.

Conclusion: Bremelanotide was safe and well tolerated and demonstrated significant improvement in efficacy vs placebo in the phase 2b trial. The multiple responder analyses offer a valuable approach for determining clinically important effects of bremelanotide for HSDD and FSAD. **Althof S, Derogatis LR, Greenberg S, et al. Responder Analyses from a Phase 2b Dose-Ranging Study of Bremelanotide. J Sex Med 2019;16:1226–1235.**

Key Words: Female Sexual Dysfunction; Hypoactive Sexual Desire Disorder; Bremelanotide; Responder Analyses; Minimal Clinically Important Difference

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[1]Case Western Reserve University School of Medicine, Department of Psychiatry, Cleveland, OH, USA;

[2]Maryland Center for Sexual Health, Lutherville, MD, USA;

[3]S. Greenberg Statistical Consulting Inc, Berkeley, CA, USA;

[4]University of Virginia, Department of Psychiatry, Charlottesville, VA, USA;

[5]Palatin Technologies, Inc, Cranbury, NJ, USA

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INTRODUCTION

The goal of a responder analysis is to determine whether changes observed during a clinical study are clinically meaningful, which is particularly useful when evaluating subjective primary and secondary endpoints. In general, participants report (through interview or via a patient-reported outcome [PRO] instrument) whether or not they have experienced a change in their condition as a result of treatment, then rate the change on a Likert-type scale that allows for worsening, no change, or improvement. Individuals whose scores exceed an a priori responder definition are classified as responders. The proportion of responders is then compared between treatment and placebo arms and a statistically significant higher response rate in the active treatment arm is considered evidence of a clinically meaningful treatment benefit. Responder analyses are recommended by the US Food and Drug Administration in its Guidance to Industry on Patient-Reported Outcome Measures,[1] which also strongly encourages the use of an a priori responder definition based on the smallest change in score that would likely be important from a patient's or clinician's perspective.[2–4] When connected to clinical anchors, this change is referred to as the minimal clinically important difference (MCID).

Bremelanotide is an investigational cyclic heptapeptide agonist of the melanocortin-4-receptor. As an analog of the neuropeptide, α-melanocyte-stimulating hormone, bremelanotide indirectly activates dopaminergic neurons believed to be involved in regulating sexual responses such as desire and arousal.[5,6] In a large, controlled, phase 2b, dose-finding trial, healthy, premenopausal women with hypoactive sexual desire disorder (HSDD) and/or female sexual arousal disorder (FSAD) were randomized for 3 months to 3 different doses of bremelanotide or placebo, self-administered subcutaneously on an outpatient, on-demand basis. After 12 weeks of treatment, bremelanotide (relative to placebo) was associated with an increase in sexual desire and arousal, a decrease in associated personal distress, and an increase in the number of satisfying sexual events (SSEs) as measured by changes observed on several validated PRO measures. The trial met its primary endpoint, as well as multiple secondary endpoints, and the main safety and efficacy findings from this study have been previously reported.[7] Here we report the results of a responder analysis of key efficacy data from this trial in an effort to determine whether the statistically significant improvements in sexual function observed represent clinically meaningful outcomes for patients (ClinicalTrials.gov identifier NCT01382719).

METHODS

Study Participants

The study comprised healthy, premenopausal (according to the Stages of Reproductive Aging Workshop criteria), nonpregnant women ≥21 years old with HSDD, FSAD, or a combination of these disorders for ≥6 months before the start of the study. Participants were required to have been diagnosed by a qualified clinician using a diagnostic interview and to have a total score <26.5 on the Female Sexual Function Index (FSFI), indicating sexual dysfunction, and a total score >18 on the Female Sexual Distress Scale—Desire/Arousal/Orgasm (FSDS-DAO), indicating sexually related distress.[8–11] They were also required to have experienced "normal" sexual function at some point in the past for ≥2 years, be currently in a monogamous relationship of ≥6-months' duration, and be willing to be sexually active with their partner ≥1 time/month during the study. Women with unstable or uncontrolled medical conditions and those with a history of unresolved sexual trauma or abuse were excluded from participating. Patients were excluded if they used any of the following types of medications: any implanted or injected testosterone product within 6 months of screening, neuroleptic drugs, lithium, antidepressants, mood stabilizers, benzodiazepines, cognitive enhancers, γ-aminobutyric acid agonists, or any other prescription, nonprescription, herbal, or nutritional supplement known to affect sexual arousal or desire within 3 months of screening. They must also not have had any topical testosterone within 7 days of screening, and must have agreed to remain off testosterone treatment for the duration of the study. Treatment for depression or psychosis within the preceding 6 months or current psychotherapy for FSD were also causes for exclusion.

Study Design

Subjects were enrolled at 67 sites (64 in the United States, 3 in Canada). All participants underwent a 4-week, no-treatment screening/qualification period, followed by a 4-week, single-blind, self-dosing (placebo-only) period to establish baseline level of symptoms. Eligible subjects were then enrolled into a 12-week, double-blind treatment period and randomized, with equal allocation, to placebo or 3 different doses of bremelanotide (0.75, 1.25, or 1.75 mg) using an interactive voice/web (Internet) response system (IVRS/IWRS, United BioSource, Blue Bell, PA, USA). The randomization scheme was generated using random permuted blocks without regard to investigative site, and stratified by diagnosis (FSAD only, HSDD only, or mixed FSAD/HSDD). The randomization code and starting seed were generated and maintained by the IVRS/IWRS vendor and were not available to the sponsor, sites, or subjects until the database had been locked, except when unblinding was required in the regulatory reporting of serious adverse events or for other safety-related reasons.

Bremelanotide or matching placebo was provided in prefilled syringes as an aqueous solution (0.3 mL). All drug syringes and drug kits, whether active or placebo, single- or double-blind, were identical in appearance and labeling to protect the blinding. During the treatment period, subjects were instructed to self-administer the blinded study drug by subcutaneous injection into the anterior thigh or abdomen on an on-demand basis approximately 45 minutes before anticipated sexual activity, and

not to exceed 1 dose per day or 16 doses during each 4-week period. Participants were assessed every 4 weeks except for SSEs, which were assessed continuously. End of study (EOS) was defined to be the last 4-week period of double-blind study drug administration for each subject.

PRO Instruments Used to Compute MCIDs

Several PRO instruments were used in this study both for screening and for measuring change.

Female Sexual Function Index (FSFI)

The FSFI is a 19-item validated measure of female sexual function consisting of 6 domains: desire, arousal, lubrication, orgasm, satisfaction, and pain.[8,9] Scores for the arousal, lubrication, orgasm, and pain domains range from 0 to 6 using Likert-type scales; scores for desire and satisfaction domains range from 1.2 to 6.0 and from 0.8 to 6.0, respectively. The total score is the sum of the domain scores and ranges from 2 to 36, and the recall period is the past 4 weeks. Higher scores indicate a greater level of sexual function. The FSFI was completed at 4-week intervals during clinic visits.

Female Sexual Distress Scale—Desire/Arousal/Orgasm (FSDS-DAO)

The FSDS-DAO is a 15-item self-assessment of the severity of sexually related personal distress, based on 2 well-validated PRO instruments, the FSDS[10] and FSDS-Revised (FSDS-R).[11] The 15-item FSDS-DAO retains the 13 items from FSDS-R, and includes 2 new items that ask women to rate their level of distress related to arousal and orgasm. As with previous versions of the FSDS, participant responses to "How often did you feel concerned with difficulties with sexual arousal?" and "How often did you feel frustrated by problems with orgasm?" are provided using a Likert-type scale and range from 0 (never) to 4 (always). Subjects who met eligibility criteria completed the FSDS-DAO with a 30-day recall at baseline, and at visits 2, 5, 10, 11, and 12. The total score is calculated as the sum of the responses and ranges from 0 to 60; with higher scores indicating a greater level of distress. Question 13 (Q13) requests a self-rating for being "bothered by low sexual desire." Questions 14 and 15 (Q14 and Q15), 2 new items in the FSDS-DAO, request a self-rating for being "concerned by difficulties with sexual arousal" and "frustrated by problems with orgasm," respectively. The FSDS-DAO was completed at 4-week intervals during clinic visits. Decreases in FSDS-DAO total score and individual item scores indicate improvement.

Female Sexual Encounter Profile—Revised (FSEP-R)

The Female Sexual Encounter Profile—Revised (FSEP-R) is a 10-item instrument that is designed to assess sexual encounters, including initiation, level of desire, satisfaction with arousal, lubrication, arousal, ability to achieve orgasm, and satisfaction with the sexual encounter.[12] A "sexual encounter" is defined as any activity involving sexual contact with genitalia and/or oral mucosa, and includes intercourse, oral sex, and masturbation by self or a partner. Question 10 (Q10) on the FSEP-R is "Did you consider this sexual encounter satisfactory for you? (yes, no)." A satisfying sexual encounter is defined as an encounter where the subject marked "yes" as the answer to Q10. The FSEP-R was completed at home, within 24 hours after each sexual encounter whether or not study drug was used before that encounter; as this assessment can be considered more of a "patient diary," it is not a validated measure. All encounters were included in the analysis regardless of whether study drug was used before the encounter.

General Assessment Questionnaire (GAQ)

The General Assessment Questionnaire (GAQ) consists of 4 items related to level of satisfaction (satisfaction with arousal, desire, degree of benefit while on study drug, and impact of taking study drug on relationship with partner). Responses are selected on a 7-point numeric rating scale from 1 (very much worse) to 7 (very much better), with 4 representing "no change." A score $\geq$5 indicates benefit. Question 3 (Q3) asked, "Compared to the start of the study (before taking the study drug), to what degree do you think you benefited from taking the study drug?" The GAQ was completed in the clinic at visits 5, 10, 11, and 12, thus providing a monthly appraisal of the subject's overall assessment of study drug benefit compared with study start. Women with a score $\geq$5 on Q3 of the GAQ at EOS were considered responders, and those who scored $<$5 were considered nonresponders.

Responder Analyses

Responder analyses were performed for the change from baseline to EOS for the following 7 PRO-based endpoints: 1) change from baseline to EOS in desire, as measured by the change in response on FSFI-desire domain (Q1—Q2); 2) change from baseline to EOS in arousal, as measured by the change in response on FSFI-arousal domain (Q3—Q6); 3) change in the degree of feeling bothered by low sexual desire (FSDS-DAO item 13); 4) change in the level of concern over difficulty with sexual arousal (FSDS-DAO item 14); 5) change from baseline to EOS in total score on the FSFI; 6) change from baseline to EOS in total score on the FSDS-DAO; and 7) change from baseline to EOS in number of SSEs, as indicated by the change in the number of "yes" responses to Q10 on the FSEP-R.

For the protocol-specified historically anchored responder analyses, expert opinion was consulted to obtain MCID estimates for FSFI total score, FSDS-DAO total score, and SSEs per 28 days/4 weeks. For completeness, all 7 endpoints were also evaluated post hoc by self-assessment, receiver operating characteristic (ROC) analysis, and/or cumulative distribution function (CDF) analysis. Self-assessment was based on responses to Q3 on the GAQ (degree of benefit from study drug). ROC curves were used to compute the MCID that maximized the sum of sensitivity and specificity for each endpoint in predicting

Table 1. Baseline demographic characteristics (mITT population)

Characteristic	Placebo (N = 91)	All BMT (N = 236)
Age, yr, mean (SD)	36.7 (7.7)	37.3 (7.3)
Race, n (%)		
White	72 (79)	169 (72)
Black	16 (18)	57 (24)
Other	3 (3)	10 (4)
Diagnosis, n (%)		
FSAD	3 (3)	8 (3)
HSDD	23 (25)	52 (22)
Mixed	65 (71)	176 (75)
Primary diagnosis, if mixed		
Number	65	175*
Primary: FSAD, n (%)	12 (18)	22 (13)
Primary: HSDD, n (%)	53 (82)	153 (87)

BMT = bremelanotide; FSAD = female sexual arousal disorder; HSDD = hypoactive sexual desire disorder; mITT = modified intention to treat; SD = standard deviation.
*1 subject who received bremelanotide 1.25 mg was missing data.

benefit. These MCIDs served as anchors for the responder analyses. The value of the area under the ROC curve ranged from 0 to 1 and provided a measure of the endpoint's ability to discriminate between a responder and a nonresponder (as defined by GAQ Q3 $\geq$5 vs <5). As a general rule, an area under the ROC curve $\leq$0.5 suggests no discrimination on that endpoint between those who do and do not respond, and areas of 0.7−<0.8, 0.8−<0.9, and $\geq$0.9 are considered acceptable, excellent, and outstanding discrimination, respectively.[13] The CDF of the percentage of participants achieving a given score or better for each endpoint was plotted for each treatment group, and the distribution functions were evaluated statistically using Kolmogorov−Smirnov and Kuiper tests for each dose vs placebo.

Statistical Analysis

Summaries and statistical analyses were performed using PC SAS 9.2 and 9.3 (SAS Institute, Cary, NC, USA) under Windows XP Pro SP3, 7, and 8 platforms (Microsoft, Redmond, WA, USA). The percentages of responders in each bremelanotide group were compared with those of the placebo group. Odds ratios, associated 95% confidence intervals (using normal approximations), and P values in the analyses that included all diagnoses were based on a Cochran−Mantel−Haenszel test stratified by diagnosis (HSDD only vs all others, as defined in the randomization). Analyses of the diagnosis subgroups were done using an unadjusted χ^2 test. All statistical tests were 2-sided and performed at the $\alpha = 0.05$ significance level.

Ethical Conduct

The study was conducted in accordance with Good Clinical Practice requirements as described in guidelines of the International Conference on Harmonisation of Technical Requirements of Pharmaceuticals for Human Use and in the Declaration of Helsinki. Each study site was reviewed by a central or local Institutional Review Board or Ethics Committee. Before any study procedures were initiated, written informed consent was obtained from each participant.

RESULTS

Study Participants

In all, 397 women were randomized, 394 received double-blind study drug, and 327 were included in the modified intention-to-treat (mITT) population (ie, those who provided post-baseline efficacy data). Baseline demographics and characteristics for the mITT population are shown in Table 1. Overall, 74% of subjects had mixed HSDD/FSAD, 23% had HSDD only, and 3% had FSAD only. Among those with a mixed diagnosis, 86% had HSDD as their primary diagnosis.

Historically Anchored Responder Analysis

This was a prespecified analysis conducted for FSFI total score, FSDS-DAO total score, and SSEs using a percent responder analysis anchored to historical estimates of MCIDs based on expert

Table 2. MCIDs for responder efficacy endpoints (ROC curves using all diagnoses)

Measure (change in)	Theoretical range for change*	Historical anchors	MCID
FSFI-desire domain	−4.8 to +4.8	+0.6	+0.6
FSDS-DAO item 13 (feeling bothered by low sexual desire)	−4 to +4	−1	−1
FSFI-arousal domain	−6.0 to +6.0	ND	+0.6 or +0.9†
FSDS-DAO item 14 (concerned by difficulty with sexual arousal)	−4 to +4	−1	−1
FSFI total score	−34 to +34	+4	+2.1
FSDS-DAO total score	−60 to +60	−7	−7
Number of SSEs	N/A	+1	+1

The MCIDs and historical anchors should be interpreted in the context of the FSFI domain and FSDS-DAO question scales described in the section titled PRO Instruments Used to Compute MCIDs.
FSDS-DAO = Female Sexual Distress Scale−Desire/Arousal/Orgasm; FSFI = Female Sexual Function Index; MCID = minimal clinically important difference; N/A = not available; ND = not defined; ROC = receiver operating characteristic; SSE = satisfying sexual event.
*In the general population. Only subsets of these ranges are possible in this study because of entry requirements based on these questionnaires.
†For this endpoint, 2 different values maximized the sum of sensitivity and specificity; both are presented.

Table 3. Responder analyses based on MCIDs (mITT population; all diagnoses pooled)

Endpoint	Placebo (N = 91)	BMT 1.75 mg (N = 74)	Odds ratio, (95% CI)	*P* value*
FSFI total score				
% Responders	46.2	68.9	2.53 (1.33–4.81)	.0044
Absolute difference	NA	22.8		
FSDS-DAO total score				
% Responders	45.1	68.9	2.66 (1.40–5.04)	.0024
Absolute difference	NA	23.9		
Number of SSEs				
% Responders	37.4	54.8	2.01 (1.08–3.77)	.0280
Absolute difference	NA	17.4		

BMT = bremelanotide; FSDS-DAO = Female Sexual Distress Scale–Desire/Arousal/Orgasm; FSFI = Female Sexual Function Index; MCID = minimal clinically important difference; mITT = modified intention to treat; NA = not available; SSE = satisfying sexual event.
*Cochran–Mantel–Haenszel test, stratified by diagnosis. The FSAD-only and mixed FSAD/HSDD strata were pooled due to the small sample size of the FSAD-only group.

opinion, which are provided in Table 2. The historically anchored responder analysis for the key endpoints of FSFI total score, FSDS-DAO total score, and number of SSEs demonstrated a dose-response effect, with a significantly greater percentage of participants in the bremelanotide 1.75 mg group showing a response compared with those receiving placebo. Since the historical anchors for the FSDS-DAO total score and number of SSEs had values identical to the computed MCIDs, the results for these 2 endpoints in the historical anchored responder analysis are identical to those provided in Table 2. For the FSFI total score, the historically based cut-off value used was +4 (vs the computed MCID of +2.1). The bremelanotide 1.75 mg dose was selected as the dose for phase 3 registration studies, as it provided the most optimal efficacy, with an acceptable safety profile.[7]

Responder Analyses Based on MCIDs

The bremelanotide 1.75 mg dose group had a statistically significantly greater percentage of responders than the placebo group, pooled across all diagnoses, for FSFI total score, FSDS-DAO total score, and number of SSEs (Table 3). Among subjects with a diagnosis of HSDD only, statistically significantly greater percentages of responders in the bremelanotide 1.75 mg group vs the placebo group was observed for FSFI total score (66.7% vs 30.4%; $P = .0281$) and FSDS-DAO total score (80.0% vs 34.8%; $P = .0064$), but not for the number of SSEs (60.0% vs 30.4%; $P = .0712$).

GAQ Q3 Responder Analysis

The GAQ Q3 responder analysis demonstrated a clear drug effect. As shown in Table 4, 79.7% of participants were self-assessed responders (GAQ Q3 score ≥5) in the bremelanotide 1.75 mg group, while 48.4% were responders in the placebo group. Results were similar when evaluating the various diagnosis subgroups.

Mean and median changes in the 7 responder efficacy endpoints were consistently more favorable for participants with

Table 4. Responders by treatment group based on GAQ Q3 self-assessment (mITT population)

Population	Treatment group	N	Responders GAQ Q3 score ≥5, n (%)	Absolute difference, %	Odds ratio (95% CI)	*P* value
All diagnoses						
	Placebo	91	44 (48.4)	31.4	4.16 (2.06–8.38)	<.0001*
	BMT 1.75 mg	74	59 (79.7)			
HSDD only						
	Placebo	23	11 (47.8)	25.5	3.00 (0.73–12.25)	.1196†
	BMT 1.75 mg	15	11 (73.3)			
HSDD as primary diagnosis						
	Placebo	76	36 (47.4)	32.0	4.27 (2.00–9.12)	.0001†
	BMT 1.75 mg	63	50 (79.4)			

BMT = bremelanotide; GAQ = General Assessment Questionnaire; HSDD = hypoactive sexual desire disorder; mITT = modified intention to treat; Q = question.
*Cochran–Mantel–Haenszel test, stratified by diagnosis.
†Unadjusted $\chi 2$ test.

Table 5. Change from baseline in combined treatment groups based on subject GAQ Q3 assessment (mITT population; all diagnoses pooled)

Endpoint	GAQ Q3 score*	Number (%) in category	Change, baseline to EOS	
			Mean	Median
Change in FSFI-desire domain (N = 327)	<5	122 (37.3)	0.09	0.0
	≥5	205 (62.7)	0.80	0.6
Change in FSDS-DAO score item 13 (feeling bothered by low sexual desire) (N = 327)†	<5	122 (37.3)	−0.1	0
	≥5	205 (62.7)	−1.0	−1
Change in FSFI-arousal domain (N = 327)	<5	122 (37.3)	0.01	0.0
	≥5	205 (62.7)	1.01	0.9
Change in FSDS-DAO score item 14 (concern by difficulty with sexual arousal) (N = 327)†	<5	122 (37.3)	0.0	0
	≥5	205 (62.7)	−1.0	−1
Change in total FSFI (N = 327)	<5	122 (37.3)	−0.18	−0.1
	≥5	205 (62.7)	4.14	3.8
Change in total FSDS-DAO (N = 327)†	<5	122 (37.3)	−2.4	−1
	≥5	205 (62.7)	−12.8	−12
Change in SSEs (N = 324)	<5	120 (37.0)	−0.2	0
	≥5	204 (63.0)	1.0	1

EOS = end of study; FSDS DAO = Female Sexual Distress Scale—Desire/Arousal/Orgasm; FSFI = Female Sexual Function Index; GAQ = General Assessment Questionnaire; mITT = modified intention to treat; Q = question; SSE = satisfying sexual event.
*Score ≥5 = responder.
†Decrease in an FSDS DAO endpoint represents an improvement, whereas for all other endpoints, an increase represents an improvement.

GAQ Q3 ≥5 than for those with GAQ Q3 <5 (Table 5), including the FSFI-desire domain and FSDS-DAO item 13, which represent 2 key aspects of the HSDD diagnosis, low desire and distress associated with low desire, respectively. Results were similar for the HSDD only group.

ROC Analysis of Efficacy Response

The ROC curves for participants pooled across diagnoses showed that GAQ Q3 is predictive of a change in 6 of the 7 efficacy endpoints, as indicated by an area under the ROC curve (AUC) value of ≥0.7; only the number of SSEs showed a lower predictive value (ie, AUC ≤0.7). The clinical significance of the results (based on ROC curves and anchoring) across diagnoses were "acceptable" for all responder endpoints other than number of SSEs. Results from ROC data for each diagnosis group were generally consistent with the ROC data across diagnoses (Table 6).

Responder Analysis Based on MCIDs

Using the MCIDs determined above, the bremelanotide 1.75 mg dose showed statistical significance in all 7 endpoints when compared with placebo across all diagnoses ($P \leq .03$) (Table 7).

Table 6. AUC from ROC curves predicting benefit (GAQ Q3 ≥5) as a function of change in responder efficacy parameters (mITT population)

Change from baseline to EOS in	All diagnoses (N = 327)	HSDD only (N = 75)	Primary HSDD (N = 281)
FSFI-desire domain	0.71	0.66	0.70
FSDS-DAO item 13 (feeling bothered by low sexual desire)	0.73	0.69	0.73
FSFI-arousal domain	0.75	0.81	0.74
FSDS-DAO item 14 (concerned by difficulty with sexual arousal)	0.74	0.66	0.74
FSFI total score	0.74	0.80	0.73
FSDS-DAO total score	0.75	0.76	0.76
Number of SSEs*	0.64	0.66	0.63

AUC = area under the ROC curve; EOS = end of study; FSDS-DAO = Female Sexual Distress Scale—Desire/Arousal/Orgasm; FSFI = Female Sexual Function Index; GAQ = General Assessment Questionnaire; HSDD = hypoactive sexual desire disorder; mITT = modified intent-to-treat; ROC = receiver operating characteristic; SSE = satisfying sexual event.
*N = 324 for number of SSEs category only.

Table 7. Responder analyses based on MCID (mITT population; all diagnoses)

Endpoint: change in	Cutoff value for success (sensitivity, specificity, %)*	Treatment group (placebo or BMT dose)	Responders, n/N (%)	Absolute difference	Odds ratio (95% CI)	*P* value vs placebo†
FSFI-desire domain	+0.6 (71.7, 64.8)	Placebo	48/91 (52.7)			—
		BMT 1.75 mg	57/74 (77.0)	24.3	3.01 (1.52–5.96)	.0013
FSDS-DAO item 13 (feeling bothered by low sexual desire)	−1 (70.2, 71.3)	Placebo	41/91 (45.1)			—
		BMT 1.75 mg	53/74 (71.6)	26.6	3.13 (1.62–6.02)	.0006
FSFI-arousal domain	+0.6 (67.3, 70.5)	Placebo	43/91 (47.3)			—
		BMT 1.75 mg	50/74 (67.6)	20.3	2.28 (1.21–4.30)	.0105
	+0.9 (57.6, 82.0)	Placebo	31/91 (34.1)			—
		BMT 1.75 mg	44/74 (59.5)	25.4	2.78 (1.47–5.24)	.0014
FSDS-DAO item 14 (concerned by difficulty with sexual arousal)	−1 (65.9, 77.0)	Placebo	40/91 (44.0)			—
		BMT 1.75 mg	48/74 (64.9)	20.9	2.36 (1.26–4.44)	.0073
FSFI total score	+2.1 (68.3, 68.9)	Placebo	42/91 (46.2)			—
		BMT 1.75 mg	51/74 (68.9)	22.8	2.53 (1.33–4.81)	.0044
FSDS-DAO total score	−7 (70.2, 70.5)	Placebo	41/91 (45.1)			—
		BMT 1.75 mg	51/74 (68.9)	23.9	2.66 (1.40–5.04)	.0024
Number of SSEs	+1 (54.9, 75.0)	Placebo	34/91 (37.4)			—
		BMT 1.75 mg	40/73 (54.8)	17.4	2.01 (1.08–3.77)	.0280

BMT = bremelanotide; FSDS-DAO = Female Sexual Distress Scale—Desire/Arousal/Orgasm; FSFI = Female Sexual Function Index; MCID = minimal clinically important difference; mITT = modified intent-to-treat; SSE = sexually satisfying event.
*When the MCID could be chosen as 1 of 2 values, both are shown.
†Cochran–Mantel–Haenszel test, stratified by diagnosis.

For subjects with a primary diagnosis of HSDD, similar analyses were performed for the desire scores, total scores, and SSE endpoints using the MCIDs derived from that subgroup. A statistically significant difference was shown for the bremelanotide 1.75 mg vs placebo for changes in all 5 endpoints assessed in the subjects with a primary diagnosis of HSDD ($P \leq .014$, data not shown).

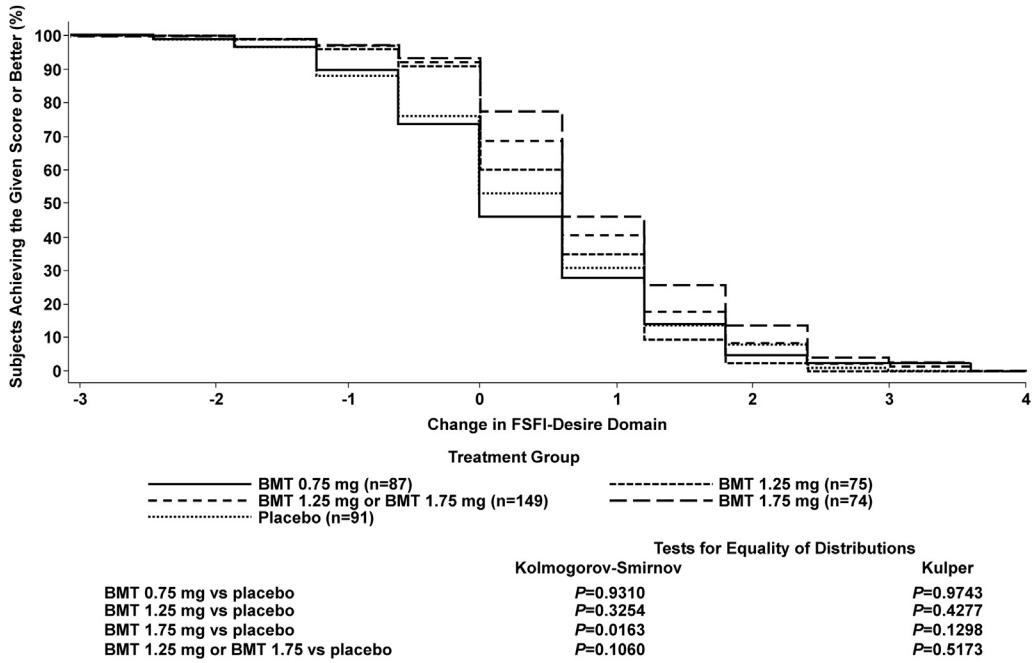

Figure 1. Cumulative distribution functions for the FSFI-desire domain. BMT = bremelanotide; FSFI = Female Sexual Function Index.

Table 8. Tests for equality of distributions for BMT 1.75 mg vs placebo (mITT population)

	P value vs placebo	
Change from baseline to EOS in	Kolmogorov-Smirnov	Kuiper
FSFI-desire domain	.0163	.1298
FSDS-DAO item 13 (feeling bothered by low sexual desire)	.0063	.0489
FSFI-arousal domain	.0104	.0659
FSDS-DAO item 14 (concerned by difficulty with sexual arousal)	.0564	.1976
FSFI total score	.0087	.0568
FSDS-DAO total score	.0005	.0050
Number of SSEs	.1705	.5399

BMT = bremelanotide; EOS = end of study; FSDS-DAO = Female Sexual Distress Scale—Desire/Arousal/ Orgasm; FSFI = Female Sexual Function Index; mITT = modified intent-to-treat; SSE = satisfying sexual event.

CDFs of Response

The CDFs for the FSFI-desire domain are presented in Figure 1, which demonstrates the consistency of response across various cutoff values. The CDF curves for the other endpoints similarly illustrate the consistency of response across various cutoff values (data not shown).

Except for the changes from baseline to EOS in FSDS-DAO item 14 (concerned by difficulty with sexual arousal) and number of SSEs, all other endpoints showed good separation between bremelanotide 1.75 mg and placebo, indicating the consistency of analyses based on the CDFs (Table 8) with those based on the study endpoints.

DISCUSSION

In this phase 2b study of premenopausal women with HSDD and/or FSAD, bremelanotide, self-administered subcutaneously on an on-demand basis, demonstrated greater responder rates vs placebo as defined by self-reported global benefit, by MCIDs representing expert opinion, and by MCIDs derived from ROC curves. In all the analyses, the responder rate attained statistical significance for the bremelanotide 1.75 mg group vs the placebo group.

Responder analysis of 7 endpoints, including key clinical endpoints that are most associated with HSDD (FSFI-desire domain and FSDS-DAO desire item 13 scores) and endpoints of FSFI arousal and total score, and FSDS-DAO scores for concern by difficulty with arousal and total score showed a robust placebo-subtracted response, indicating that the clinical questionnaires measuring efficacy coincided with the participant's self-assessment of benefit while on study drug. The ROC curves showed that a participant's self -assessment of benefit (as measured using responses from the GAQ Q3) was predictive of an effect in 6 of the 7 endpoints; only the number of SSEs had a lower predictive value. The CDFs showed a clear separation of response between bremelanotide 1.75 mg and placebo except for changes in the FSDS-DAO arousal score and number of SSEs.

It is important to note that in this study the MCIDs obtained by ROC curve analyses were based on the change from using single-blind placebo (during the baseline period) to using double-blind study drug; thus, the change accrued was in addition to any benefit already gained from placebo, which was substantial as demonstrated by comparing data from the single-blind placebo month with the preceding no-treatment month. This comparison showed that in each of several key FSD measures, the mean response to placebo met or exceeded the relevant ROC curve-derived MCID. When comparing the change from baseline to EOS (among subjects with postbaseline data), there was a strong correlation between the anchor variable (GAQ Q3) and multiple different efficacy measures. For the GAQ Q3 $\geq$5 group (the responder group), the mean FSFI total score increased by 4.14, and the mean FSDS-DAO total score change was -12.80, both of which were approximately double the corresponding MCID (+2.1 and -7, respectively). The mean number of SSEs increased by 1.0, matching the MCID. For the FSFI-desire domain and FSDS-DAO Item 13, the mean changes from baseline to EOS for the GAQ Q3 $\geq$5 groups were +0.8 (more than the MCID, which was +0.6) and -1.0 (matching the MCID), respectively. These findings not only confirm the strong placebo effect commonly seen in clinical studies with patient-reported endpoint measures, but most importantly, they highlight the clinically relevant improvements associated with bremelanotide treatment.

This study has some limitations. First, the study included only premenopausal women with a clinical diagnosis of HSDD and/or FSAD. Second, the development of responder thresholds and the comparison of responder rates for different treatments, as defined by these thresholds, were based on data from the same clinical trial. Further research is needed to confirm these findings in clinical trials and other studies of women with FSD. However, it is encouraging that the a priori expert opinion for thresholds and the empirically derived criteria were comparable.

Overall, the MCIDs reported here can be viewed as providing a context for judging the clinical relevance of numerical changes in FSFI and FSDS-DAO total scores and secondary domain/item scores related to sexual desire and arousal. By this interpretation, the majority of women in the bremelanotide 1.75 mg group had clinically relevant improvement across a variety of FSD measures,

with 77.0% reporting an improvement in the FSFI-desire domain (vs 52.7% in the placebo group) and 71.6% reporting a decrease in distress per FSDS-DAO Item 13 (vs 45.1% in the placebo group). Responder definitions derived from empirical evidence may offer a valuable approach for determining clinically important effects of new treatments for FSD. Our results are also consistent with the limited utility of number of SSEs as a clinical endpoint. Similarly, in the ROC analysis, the number of SSEs showed a lower predictive value (Table 6) and there was less separation between the bremelanotide 1.75 mg and placebo groups for this endpoint in the CDF analysis (Table 8). These findings could relate in part to the subjective nature of patient-reported SSEs, a downstream measure of treatment effects, as a clinical endpoint. In this regard, it is notable that SSEs are not included as a diagnostic criterion for HSDD or FSAD; indeed, women with higher desire may, or may not, have more SSEs, whereas those with HSDD may have satisfying events, but low desire. As such, the inclusion of instruments that more reliably assess the key aspects of HSDD, sexual desire and arousal, and distress (ie, FSFI, FSDS-DAO) will be important in future studies of FSD.

Together with the mean and median change from baseline data observed in the primary and most secondary efficacy analyses, the responder analysis demonstrates that bremelanotide has clear clinical benefit. Statistically significant superiority of bremelanotide over placebo in efficacy has been demonstrated, and adverse events from the study were collected; both are detailed in a separate publication.[7] Bremelanotide at a dose of 1.75 mg, self-injected subcutaneously, was shown to improve sexual function and decrease distress associated with low sexual desire, which was measured using the validated and widely accepted FSFI and FSDS-DAO. Clinical benefit and efficacy were demonstrated across multiple domains of sexual function in women with HSDD alone and the population with mixed FSAD/HSDD.

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Corresponding Author: Stanley Althof, PhD, 1515 N Flagler Drive, Suite 540, West Palm Beach, FL 33401; Tel: (561) 822-5454; Fax: (561) 822-5458; E-mail: Stanley.Althof@case.edu

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STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design
(b) Acquisition of Data
(c) Analysis and Interpretation of Data

Category 2

(a) Drafting the Article
(b) Revising It for Intellectual Content

Category 3

(a) Final Approval of the Completed Article

Statement of Authorship: Conceptualization, Methodology, Investigation, Resources, Writing ? Original Draft, Writing ? Review & Editing, Funding Acquisition, Data Curation: S. A., L.R.D., S.G., A.H.C., R.J., J.L., and C.S. All authors contributed to the research, writing, and reviewing of all drafts of the manuscript, and approved the final version.

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