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Developing Clinically Meaningful Responder Thresholds for Primary Endpoints for Clinical Trials in Premenopausal Women With Hypoactive Sexual Desire Disorder

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Background

- The self-reported prevalence of any sexual problems is approximately 43% among women ≥18 years old, and these problems are often accompanied by distress[1]
- Hypoactive sexual desire disorder (HSDD), which describes a lack of motivation for sexual activity or loss of desire to initiate/participate in sexual activity accompanied by significant personal distress, is one of the most common sexual problems reported by women[2]
  - 8.9% of women between the ages of 18–44 years and 12.3% between 45 and 64 years are affected by HSDD
  - HSDD impacts women's emotional and social functioning, and their relationship with their partners
  - HSDD is under-recognized and under-treated
- Bremelanotide, an investigational drug for the treatment for HSDD in premenopausal women, resulted in significantly greater improvements relative to placebo on the Female Sexual Function Index Desire domain (FSFI-D) and on item 13 of the Female Sexual Distress Scale–Desire/Arousal/Orgasm (FSDS-DAO-Q13) scale in two clinical trials (RECONNECT)[3]
- For clinical trials that evaluate efficacy endpoints based on patient-reported outcomes, including those in patients with HSDD, guidelines are needed for interpreting clinically meaningful responses that can define treatment responders[4,5]
  - Such guidelines and definitions may assist clinicians and regulatory agencies in appropriately evaluating the clinical significance of treatment differences

Objectives

- To identify clinically meaningful responses for the FSFI-D and the FSDS-DAO-Q13 scores using an anchor-based approach, and to provide support for validity of responder definitions on these measures

Methods

Study Design

- An Independent Anchor Assessment Committee (IAAC) was established to conduct a blinded, psychometric analysis of data collected from two Phase 3 studies (RECONNECT) of bremelanotide
- An anchor-based approach was used that relied on external criteria ("anchors") that were independent of the sample[6]

RECONNECT Clinical Trials

- The two RECONNECT studies, of identical, randomized, placebo-controlled design, evaluated the safety and efficacy of bremelanotide for the treatment of HSDD with or without decreased arousal[3,7]
- Bremelanotide or placebo was administered subcutaneously on an as-desired basis in 1202 premenopausal women during a 24-week double-blind period
- Co-primary endpoints in both trials were:
  - Change from baseline on the FSFI-D
  - Change from baseline on the FSDS-DAO-Q13, which assesses "feeling bothered by low sexual desire"
- The FSFI is a 19-item measure of female sexual function consisting of six domains: Desire, Arousal, Lubrication, Orgasm, Satisfaction, and Pain[8,9]
- The FSDS-DAO is based on the FSDS-R, a 13-item instrument designed to evaluate different aspects of sexual-related distress over the past 30 days[10]
  - The FSDS-DAO contains two additional questions—one item regarding arousal and one item regarding orgasm
- The trials included a post-study exit survey of 243 participants who were asked about whether they experienced a meaningful benefit from treatment

Anchors

- In the psychometric analyses for determining clinically meaningful responses, a dynamic anchor and 3 static anchors were defined
- The dynamic anchor was item 3 on the General Assessment Questionnaire (GAQ-Q3)
  - Item 3 assesses treatment benefit (ie, "Compared to the start of the study [prior to taking the study drug], to what degree do you think you benefitted from taking the study drug?")
  - The cut-off for a responder definition was determined as a response of 5 (ie, "better" or "much better")
- Static anchors were:
  - Question 9 on the Elements of Desire Questionnaire (EDQ-Q9),[11] which assesses desire and interest in sex
    - This item was thought to be most highly related to the FSFI-D subscale, and shows a moderate correlation with the FSDS-Q13 distress scale[11]
    - The cut-off for a responder definition was determined as an improvement ≥1 category on the response scale
  - Question 1 on the FSDS-DAO (FSDS-DAO-Q1), which assesses distress about sex life
    - The cut-off for a responder definition was determined as an improvement ≥1 category on the response scale
  - Question 16 on the FSFI (FSFI-Q16), which evaluates satisfaction with sex life
    - The cut-off for a responder definition for the FSFI-Q16 was determined as an improvement ≥1 category on the response scale

Analyses

- Mean and median changes from baseline to endpoint in FSFI-D and FSDS-DAO-Q13 scores were examined by responder definitions for the four anchors
- The treatment benefit items were used as anchors for confirming the responder thresholds for the primary endpoints of FSFI-D and FSDS-DAO-Q13 scores
- Results were reviewed by the IAAC and recommendations were made on responder thresholds for the FSFI-D and FSDS-DAO-Q13 scores
- Data from the post-study exit survey were used to further support the validity of the responder thresholds by evaluating the relationship between overall treatment benefit versus changes in FSFI-D and FSDS-DAO-Q13 scores
  - Percentage agreement and kappa values were calculated; a kappa value of 1=perfect agreement
- For comparison with a distribution-based approach, which relies on one-half of a standard deviation interpreted as a moderate effect size that is clinically meaningful,[12] the identified responder values were translated into effect sizes

Results

- For the treatment benefit dynamic anchor (GAQ-Q3), median and mean change scores on the FSFI-D were 0.6 and 0.85, respectively
- Similarly, the median and mean change scores on FSDS-DAO-Q13 for the GAQ-Q3 were 1.0 and 0.9, respectively

Table 1. Summary of Estimated Responder Thresholds by Anchor for Female Sexual Function Index Desire Domain (FSFI-D) and Item 13 of the Female Sexual Distress Scale–Desire/Arousal/Orgasm (FSDS-DAO-13)

Endpoint	Parameter	Anchor 1[a]	Anchor 2[b]	Anchor 3[c]	Anchor 4[d]
Change in FSFI-D	Best summary statistic for determining a meaningful responder, median	0.600	0.600	1.200	1.200
	Most informative cut point	0.600	0.600	0.600	0.600
	Meaningful responder threshold	0.600	0.600	0.600	0.600
Change in FSDS-DAO-Q13 (feeling bothered by low sexual desire)	Best summary statistic for determining a meaningful responder, median	−1.000	−1.000	−1.000	−1.000
	Most informative cut point	−1.000	−1.000	−1.000	−1.000
	Meaningful responder threshold	−1.000	−1.000	−1.000	−1.000

[a]GAQ-Q3: Compared to the start of the study (prior to taking the study drug), to what degree do you think you benefited from taking the study drug?; [b]FSDS-DAO-Q13: Distressed about your sex life; [c]FSFI-Q16: Over the past 4 weeks, how satisfied have you been with your overall sexual life?; [d]EDQ-Q9: Over the past 4 weeks, how would you rate your satisfaction with your level of desire or interest in sexual activity?

- Based on the pooled psychometric analyses, the anchor-based results supported as clinically meaningful were a 0.6 point change in FSFI-D scores (range 0.6–1.2), and a 1.0 change in FSDS-DAO-Q13 scores (range 0–4) (**Table 1**)
- For the FSFI-D, the recommended clinically meaningful thresholds of 0.6 translates into a 0.73 effect size (based on pooled standard deviation=0.83), and for the FSDS-DAO-Q13, the threshold of 1 translates into a 1.11 effect size (based on pooled standard deviation=0.91)
  - Effect sizes >0.70 are considered large[13]

Table 2. Descriptive Characteristics of Patient Survey and Significant Associations Overall: Treatment Experience by Responder Group Based on Item 3 of the General Assessment Questionnaire (GAQ-Q3)

Exit Survey	Number (%) Total (N=242)	Responder[b] (n=117)	Non-responder[c] (n=124)	Missing (n=1)	*P*[a]
During the course of the clinical study, did you BENEFIT OVERALL from the study medication and, if so, was this benefit enough to be meaningful to you?					<0.0001
No	113 (46.7)	6 (5.1)	106 (85.5)	1 (100)	
Yes, but not meaningful	30 (12.4)	17 (14.5)	13 (10.5)	0	
Yes, and meaningful	98 (40.5)	94 (80.3)	4 (3.2)	0	
Missing	1 (0.4)	0	1 (0.8)	0	

[a]Chi-square test; [b]Responders were participants who indicated an end of study score of "better," "much better," or "very much better" on GAQ-Q3; [c]Non-responders group were participants who indicated an end of study score of "same," "worse," "much worse," or "very much worse" on GAQ-Q3.

- The exit survey question on overall treatment benefit demonstrated a percentage agreement of 88% and kappa of 0.77 with the threshold ≥5 on the dynamic anchor, representing a response of "better" or "much better" and indicating excellent agreement (**Table 2**)

Table 3. Descriptive Characteristics of Patient Survey and Significant Associations: Overall Treatment Experience by Female Sexual Function Index Desire Domain (FSFI-D) Responder Groups

Exit Survey	Number (%) Total (N=242)	Responder[b] (n=99)	Non-responder[c] (n=142)	Missing (n=1)	*P*[a]
During the course of the clinical study, did you BENEFIT OVERALL from the study medication and, if so, was this benefit enough to be meaningful to you?					<0.0001
No	113 (46.7)	23 (23.2)	90 (63.4)	0	
Yes, but not meaningful	30 (12.4)	12 (12.1)	17 (12.0)	1 (100)	
Yes, and meaningful	98 (40.5)	63 (63.6)	35 (24.6)	0	
Missing	1 (0.4)	1 (1.0)	0	0	

[a]Chi-square test; [b]Responders were participants with change from baseline to end-of-study ≥0.6 in FSFI-D; [c]Non-responders were participants with change from baseline to end-of-study <0.6 in FSFI-D.

Table 4. Descriptive Characteristics of Patient Survey and Significant Associations Overall Treatment Experience by Item 13 of the Female Sexual Distress Scale–Desire/Arousal/Orgasm (FSDS-DAO-13) Responder Group

Exit Survey	Number (%) Total (N=242)	Responder[b] (n=116)	Non-responder[c] (n=125)	Missing (n=1)	*P*[a]
During the course of the clinical study, did you BENEFIT OVERALL from the study medication and, if so, was this benefit enough to be meaningful to you?					<0.0001
No	113 (46.7)	36 (31.0)	77 (61.6)	0	
Yes, but not meaningful	30 (12.4)	11 (9.5)	18 (14.4)	1 (100)	
Yes, and meaningful	98 (40.5)	68 (58.6)	30 (24.0)	0	
Missing	1 (0.4)	1 (0.9)	0	0	

[a]Chi-square test; [b]Responders were participants with change from baseline to end-of-study ≥1.0 in FSDS-DAO-Q13; [c]Non-responder were participants with change from baseline to end-of-study <1.0 in FSDS-DAO-Q13.

- The recommended responder thresholds for the FSFI-D and FSDS-R were supported by the exit survey treatment benefit question (**Tables 3 and 4**)

Conclusions

- Improvements of 0.6 and 1.0 were identified as clinically meaningful changes on the FSFI-D subscale and FSDS-DAO Question 13, respectively
  - These recommendations were based on the mean and median change in scores associated with multiple selected dynamic and static anchors
  - Estimated effect sizes of these thresholds were large
- Comparisons of mean and median change scores between responders versus non-responders using the same anchor measures further supported the clinical meaningfulness of the identified values from the phase 3 trials

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