ORIGINAL RESEARCH—FSD PHARMACOTHERAPY

Open-Label Extension Study of Flibanserin in Women with Hypoactive Sexual Desire Disorder

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ABSTRACT

Introduction. Hypoactive Sexual Desire Disorder (HSDD) is a common form of Female Sexual Dysfunction characterized by low sexual desire that causes distress or interpersonal difficulty.

Aim. This 52-week open-label extension study aimed to assess the safety and tolerability of flibanserin, a postsynaptic 5-HT_{1A} agonist/5-HT_{2A} antagonist, in women with HSDD.

Methods. Women with HSDD who had completed a trial of flibanserin or flibanserin placebo received flexible-dose flibanserin (50 or 100 mg once daily at bedtime [qhs] or 25 or 50 mg twice daily [bid]) for 52 weeks.

Main Outcome Measures. Primary end points were: proportions of women with somnolence, sedation, fatigue, dizziness, nausea, and vomiting (adverse events [AEs] known to be associated with flibanserin); discontinuations due to AEs; and serious AEs. Secondary end points included change from baseline in Female Sexual Distress Scale-Revised total and Item 13 scores and Female Sexual Function Index (FSFI) total and desire domain score scores. FSFI total scores were used to classify women into FSFI remitters (FSFI score >26.55, indicating no clinical sexual dysfunction) and FSFI non-remitters (FSFI score <26.55).

Results. Of the 1723 women who received flibanserin, 962 (55.8%) completed 12 months' treatment, and 883 women were exposed to flibanserin 100 mg qhs for ≥180 days. Somnolence, sedation, fatigue, dizziness, nausea, and vomiting were reported by 15.8, 1.6, 7.6, 6.9, 6.3, and 1.4% of participants, respectively. A total of 185 participants (10.7%) discontinued due to AEs. Serious AEs were reported by 1.2% of participants. At study end, 42% of baseline non-remitters had improved their FSFI score to remission level. The proportion of baseline FSFI remitters in remission rose from 83% at week 4 to a stable value of ~90%.

Conclusion. Flibanserin was well tolerated. Sexual function improved in women who were not FSFI remitters at baseline, and was maintained in those who were remitters at baseline. **Jayne C, Simon JA, Taylor LV, Kimura T, and Lesko LM. Open-label extension study of flibanserin in women with Hypoactive Sexual Desire Disorder. J Sex Med 2012;9:3180–3188.**

Key Words. Flibanserin; HSDD; Hypoactive Sexual Desire Disorder; Desire; Sexual Function; Safety

Introduction

Hypoactive Sexual Desire Disorder (HSDD) is defined by the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) as a persistent or recurrent deficiency or absence of sexual fantasies and desire for sexual activity that causes marked distress or interpersonal difficulty [1]. The dysfunction should not be better accounted for by another psychiatric disorder (except another sexual dysfunction) or be due exclusively to the physiological effects of a substance or general medical condition [1]. A

cross-sectional, demographically representative U.S. population-based survey conducted in 2006 found that approximately 1 in 10 premenopausal women reported low sexual desire with associated distress, which may indicate HSDD [2]. HSDD is believed to be the most common form of Female Sexual Dysfunction but remains underdiagnosed and undertreated [3–5].

Flibanserin is a postsynaptic 5-HT_{1A} agonist/5-HT_{2A} antagonist that enhances dopamine and norepinephrine activity and reduces serotonin (5-HT) activity in certain brain regions [6–9]. The drug has been hypothesized to act by redressing neurotransmitter imbalances thought to contribute to the low sexual desire of women with HSDD [9]. The efficacy and safety of flibanserin 100 mg qhs in North American premenopausal women with HSDD have been demonstrated by three 24-week randomized, double-blind placebo-controlled trials (VIOLET, DAISY, and BEGONIA) [10–12]. Flibanserin 100 mg qhs was well tolerated and associated with improvements in sexual desire and sexual function and relief of distress associated with low sexual desire [10,12].

In a randomized withdrawal trial (ROSE), premenopausal women with HSDD received 24-week open-label treatment with flibanserin and then women who met predefined enrichment criteria were randomized to receive flibanserin or placebo for 24 weeks [13]. Flibanserin treatment was well tolerated and no withdrawal reactions were observed following discontinuation [13]. Flibanserin was superior to placebo on the number of satisfying sexual events, and measures of sexual desire, overall sexual function, and sexual distress at the end of the double-blind period [13].

The aim of this study (SUNFLOWER) was to gain further data on the safety and tolerability of flibanserin in premenopausal women with HSDD.

Materials and Methods

SUNFLOWER was a 52-week open-label extension study in which North American women with HSDD who had completed a previous trial of flibanserin or flibanserin placebo received flexible-dose flibanserin treatment (50 or 100 mg qhs or 25 or 50 mg bid). The study consisted of a screening period of up to 28 days without treatment, followed by a 52-week open-label treatment period and a 4-week follow-up period after flibanserin discontinuation.

The SUNFLOWER study was conducted in accordance with the principles specified in the Declaration of Helsinki (1996 Version). There were 201 participating trial sites (178 in the United States and 23 in Canada). The Institutional Review Board at all participating centers approved the study protocols and all women gave written informed consent. Participants were compensated for their travel to the clinic.

Participants

Women were invited to be screened for entry into the SUNFLOWER study if they had completed one of the following five clinical trials of flibanserin: the randomized placebo-controlled trials VIOLET [10] (NCT00360529), DAISY [12] (NCT00360555), or DAHLIA [14] (NCT00360243), the randomized withdrawal study ROSE [13] (NCT00277914), or a pharmacokinetic study. Women who participated in, but did not complete, the ROSE study (but no other of the parent studies) could be included, provided they had indicated that they had experienced a meaningful benefit from flibanserin on discontinuation from the ROSE study. Thus the SUNFLOWER study population included women who had responded to flibanserin in the ROSE study, as well as both responders and nonresponders from randomized double-blind placebo-controlled trials.

The VIOLET, DAISY, and DAHLIA trials were randomized placebo-controlled trials of flibanserin in premenopausal women with HSDD that investigated the following dose regimens: 50 mg and 100 mg qhs in VIOLET; 25 mg and 50 mg bid (uptitrated from 50 mg qhs), and 100 mg qhs (uptitrated from 50 mg qhs) in DAISY; and 25 mg bid, 50 mg bid, and 50 mg qhs in DAHLIA [10,12,14]. In the ROSE study, premenopsual women received 24-week open-label flibanserin treatment (flexible dose of 50 mg or 100 mg/day) and then women who met predefined enrichment criteria were randomized to 24-week continued flibanserin therapy at optimized dosage or placebo for 24 weeks [13]. In the Phase II pharmacokinetic trial, premenopausal women were randomized to receive either once daily (qd) or bid open-label flibanserin treatment; the participants received flibanserin 50 mg qd or 25 mg bid on days 1–8, followed by a washout period, followed by flibanserin 100 mg qd or 50 mg bid from days 15–22. The inclusion criteria for all the parent trials required that participants were aged ≥18 years, premenopausal (defined according to the Stages of Reproductive Aging Workshop criteria [15]), and had a diagnosis of generalized acquired HSDD (according to DSM-IV-TR crite-