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A Selective Serotonin Receptor Agonist for Weight Loss and Management of Menopausal Vasomotor Symptoms in Overweight Midlife Women: a Pilot Study

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Authors' contributions –All the authors participated in the study concept and design, analysis and interpretation of data, drafting and revising the paper, and have seen and approved the final version of the manuscript. EK-Dr. Kapoor was the co-principal investigator on the study. She contributed to development of the study protocol, recruitment of participants, and their follow-up in the study. She is the primary author of the manuscript. SSF – Dr. Faubion was a co-principal investigator for the study. She and Dr. Croghan collaborated in obtaining funding for the study concept and with Drs. Croghan and Kapoor participated in the study design. She and Drs. Kapoor and Hurt were responsible for safety screening for study entry and the safety oversight of the study participants while on study. She also participated in the review and interpretation of study results, and critical revision of the manuscript for important intellectual content. RTH - participated in the study design and was responsible for safety screening for study entry and the safety oversight of the study participants while on study. He also participated in the review and interpretation of study results, and critical revision of the manuscript for important intellectual content. KF and DRS participated in the study design and were responsible for data quality checks and data analysis; they also had full access to all the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis as well as participating in the manuscript reviews and edits. SCF- reviewed the study flow, screened the study participants, oversaw all the study visits and lorcaserin treatments, as well as worked with the study clinicians and PI to address patient safety issues and with the PI and statistician to clean out the electronic data as well as provide reviews and edits to the manuscript. ITC – Dr. Croghan was a co-principal investigator on the study. She conceived the study concept and design; collaborated with Drs. Faubion and Kapoor in refining the working study design; and collaborated with Dr. Faubion in obtaining study funding. She provided administrative, technical, and material support; she, along with Drs. Faubion and Kapoor, had full oversight of the study conduct during data collection; had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; and participated in critical revision of the manuscript for important intellectual content.

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Ethics and Consent to Participate – In accordance with the Declaration of Helsinki, this study was reviewed and approved (ID 17-003060) by the Mayo Clinic Institutional Review Board (IRB). Mayo Clinic IRB approved written informed consent was obtained for all study participants prior to study participation.

Availability of Data and Materials – All data supporting the study findings are contained within this manuscript and available upon request.

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Abstract

Objective: Weight gain and vasomotor symptoms (VMS) are common complaints in midlife women going through the menopause transition. A selective serotonin 2C (5-HT_{2C}) receptor agonist, lorcaserin, that was previously FDA-approved for weight loss, has unreported observational evidence suggesting improvement in VMS with its use. The goal of this pilot study was to evaluate the efficacy of lorcaserin for weight loss and management of VMS in overweight midlife women.

Methods: This was a 24-week open label pilot study of 20 overweight midlife women, aged 45-60 years, who were experiencing severe VMS. Participants received lorcaserin at the standard dose of 10 mg twice daily for 12 weeks, followed by 12 weeks of observation off the drug. The primary outcomes were changes in weight and subjectively reported VMS.

Results: At the end of 12 weeks, mean change in weight was -2.4 kg [90% CI, (-3.2)-(-1.7), $p < 0.001$]. However, the participants returned to the baseline weight at 24 weeks. Participants also reported significant subjective improvement in VMS, with a mean $\pm$ SD change in self-reported hot flash frequency from baseline to week 12 of -5.4 ± 3.9 (decrease of 1.4 standard deviations). There was a rapid increase in the frequency of VMS within 2 weeks of discontinuation of lorcaserin with a tendency to approach the baseline frequency of VMS.

Conclusions: In addition to its weight loss-inducing effect, 5-HT_{2C} receptor modulation may have an additional beneficial effect on VMS in midlife women. A treatment option that targets both weight and VMS in midlife women is attractive.

Keywords

lorcaserin; serotonin receptor agonist; hot flash; vasomotor symptoms; obesity

Introduction

Weight gain accompanied by an increased tendency for central fat deposition is common among women in midlife.¹ These changes are a result of aging, decreasing estrogen levels after menopause, and other unique influences in menopausal women that interfere with the adoption of healthy lifestyle measures, including vasomotor symptoms (VMS).¹ Central obesity, in particular, results in several adverse metabolic consequences, including dysglycemia, dyslipidemia, hypertension, cardiovascular disease, and an increased mortality risk.²

The importance of weight management in these patients cannot be overemphasized. VMS are also a common complaint among peri- and postmenopausal women, occurring in approximately 75% of women.³ Recent data indicate that VMS last longer than originally thought, for an average of 7-10 years for frequent and/or moderate to severe VMS, and even longer for less frequent or severe VMS.⁴⁻⁶ Women with frequent and severe VMS report a significant impairment in the quality of life,⁷ sleep disturbance,⁸ depressed mood,⁹ and often

require pharmacotherapy.¹⁰ A treatment strategy targeted toward both of these common problems in midlife women, i.e., weight gain and VMS, would be desirable.

Menopausal hormone therapy (MHT) is the most effective treatment for VMS,^{11,12} but it does not typically result in weight loss.¹ Moreover, women may choose not to be on MHT, or it may be contraindicated or not a preferred treatment option in certain situations, particularly in survivors of estrogen-sensitive cancers. Nonhormone pharmacologic agents are often needed in such patients if their VMS are moderate to severe in intensity.^{12–14} Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SSNRIs), gabapentinoids, clonidine and oxybutynin are effective for treatment of VMS,^{14–17} and low dose paroxetine is the first nonhormone treatment for VMS approved by the United States Food and Drug Administration (FDA).^{13,14} However, these therapies are not associated with significant weight loss, and some may even lead to weight gain.^{18,19} Lorcaserin is a selective serotonin 2C (5-HT_{2C}) receptor agonist and is believed to promote satiety and decrease food intake by activating 5-HT_{2C} receptors on anorexigenic pro-opiomelanocortin neurons in the arcuate nucleus of the hypothalamus, although the exact mechanism of action remains unknown.^{20,21} Lorcaserin was approved by the FDA in 2012 for weight management in individuals with a body mass index (BMI) of ≥ 27 kg/m² in the presence of at least one weight-related condition such as type 2 diabetes, hypertension or dyslipidemia or in those with obesity (BMI ≥ 30 kg/m²).^{22,23}

Unreported observational evidence from studies conducted at our institution has suggested that lorcaserin use in midlife women may improve VMS. Therefore, the selective 5-HT_{2C} receptor agonist was thought to have the potential to serve a dual purpose in overweight or obese midlife women who experienced severe VMS. Based on these anecdotal observations, we conducted a pilot study to obtain preliminary data on the effectiveness of lorcaserin for weight loss and management of VMS in midlife women.

Methods

Study Overview

The present study was designed as an open-label clinical trial in which participants received 12 weeks of lorcaserin. The study was approved by the Mayo Clinic Institutional Review Board (ID 17-003060), and written informed consent was obtained for all study participants.

Setting

Participants were recruited in the Women's Health Clinic (WHC) at Mayo Clinic, Rochester, between September 2017 and June 2018. This report is based on all participants who provided consent and received study treatment (Figure 1).

Participants

Women were considered eligible for participation if they were between the ages of 45–60 years, had a BMI between 27–29.9 kg/m², and if they had at least one weight related comorbidity (in order to meet criteria for treatment with lorcaserin). In addition, they were required to report bothersome VMS, defined as 28 or more hot flashes per week that were

present for more than 30 days, and were of sufficient severity to prompt them to seek therapeutic intervention. After potential participants were identified, they completed a screening visit in the WHC. They were excluded from the study if they: did not meet the age or BMI criteria, were on a concurrent weight loss program (including weight loss medications, supplements or programs); had weight fluctuations of 20 pounds or more in past six months; had a medically unstable condition (as defined by the investigator); had a positive pregnancy test; had a known active eating disorder; were on hormone therapies or serotonergic medications; had an unstable, clinically significant psychiatric condition; were not able to provide consent to study; or had any other condition thought to hinder participation or adherence to study procedures. If deemed eligible, participants signed an informed consent. Once consented, they were asked to complete study questionnaires and a hot flash diary for a minimum of two weeks. They subsequently attended an in-person baseline visit to receive medication for the intervention phase of the study.

Interventions

Behavioral —All participants received the Mayo Clinic intervention manual “My Weight Solution.” Topics in this manual include motivational strategies, social support, goal setting strategies, nutritional recommendations and recommendations for physical activity. In addition to the physician investigators providing each participant with a copy and an overview of its contents, the physician also gave each participant a motivational message.

Lorcaserin —All participants received lorcaserin (Belviq Eisai, Tokyo, Japan) at the recommended dosage of 10 mg orally twice daily for 12 weeks.^{22,23}

Outcomes & Safety Measures

The primary outcomes for the present study included change in body weight and self-reported hot flash severity and frequency, compared to baseline. Secondary outcomes included changes in: (1) anthropometric measures; (2) body composition measurements, and (3) self-assessed quality of life, sleep and sexual function as measured by standard questionnaires.

Anthropometric Measurements—These were performed on all participants during all study visits. Height of the participant with bare feet was measured to the nearest 0.5 cm using the InBody wall-mounted vertical stadiometer. Weight was measured wearing light street clothing and no socks or shoes using the InBody scale, which was calibrated electronically. Body Mass Index (BMI) was calculated using the standard formula. Waist circumference (WC) was measured while participants were upright. A soft measuring tape was placed in a horizontal plane around the abdomen midway between the lowest rib and the superior border of the iliac crest. The tape was held snug but not compressing the skin and parallel to the floor. The measurement was made at the end of a normal expiration. Hip circumference was measured at the maximal protrusion of the buttocks. Circumferences were given as the mean of two measurements to the nearest 0.1 cm. The Waist/Hip Ratio (WHR) was calculated from the waist and hip measurements.

Hot Flash Diary—Participants were asked to rate and track their hot flashes the week prior to starting study medications (between consent visit and baseline visit); and daily through the 12 weeks of study medication; and an additional week after the end of study medication (between weeks 12 and 13). For the weeks pre-drug and post-drug, the hot flash diary was focused solely on the hot flashes, and for the weeks during drug treatment, it was combined with the drug dosing diary.

InBody Measurements—The InBody bioelectrical impedance (BIA) scale,²⁴ was used to measure the participants' weight, height, BMI, body composition analysis (total body water, body fat mass, lean body mass and visceral fat).

Questionnaires—The participants filled out questionnaires assessing menopausal symptom severity (Menopause Rating Scale-MRS)²⁵, quality of life (Linear Analogue Self-Assessment -LASA)²⁶, sexual function (Female Sexual Function Index-FSFI²⁷ and Female Sexual Distress Scale Revised, FSDS-R)²⁸ and sleep (Pittsburgh Quality of Sleep Index, PSQI).²⁹ The safety measures included (1) adverse events, (2) concomitant medication use, and (3) self-reported depression using the Center for Epidemiologic Studies Depression Scale (CES-D).^{30,31}

Study Schedule

The study timeline is summarized in Figure 2. Study visits were divided into three phases: screening, intervention, and post-intervention. All participants were in the study for 6 months. The screening phase included a pre-screen phone interview and a combined consent/screen visit. Participants were asked to complete a diary recording hot flash activity (frequency and severity) until they returned for the baseline visit. At least two weeks after the screening visit, participants returned for a baseline visit where study criteria were verified, and participants received 6 weeks of study medication- this was considered the beginning of the intervention phase. Participants returned at 6 and 12 week visits during the intervention phase, and were asked to complete a medication compliance and hot flash activity diary. After participants completed the intervention phase, they were asked to continue documenting their hot flash activity until they completed the safety phone visit with study staff. Participants were required to complete in-person study visits at weeks 6, 12 and 26 for measurement of vital signs (pulse and blood pressure), anthropometric measures and BIA in addition to providing data pertaining to QOL (LASA), female sexual function and distress (FSFI & FSDS-R), sleep (PSQI), and safety (adverse events, concomitant medication, & CES-D). In addition, during the final visit (week 26), satisfaction was measured via an end-of-study self-assessment survey.

Data Analysis

Participant characteristics were described using mean, standard deviation, minimum, and maximum for continuous variables and frequency percentages for categorical variables. The primary endpoints were the average change in weight and the number of subjectively reported hot flashes from baseline to the end of treatment at week 12. Secondary endpoints included other measures of adiposity and body composition measures (WC, BMI, body fat mass, skeletal muscle mass, percent body fat, and visceral fat level). Scores for

questionnaires assessing sexual function, sleep quality, depression and quality of life were calculated using published guidelines.^{22–25} All endpoints were analyzed as continuous variables. For each endpoint, the change from baseline was assessed using the paired t-test with a one-tailed p-value < 0.05 considered significant. In all cases 90% confidence intervals for point estimates were reported. Statistical analysis was done using SAS statistical software (SAS version 9.4; SAS Institute Inc.).

The sample-size for the present study was determined for the primary outcome of weight change from baseline to week 12. For the proposed population, we hypothesized that an intervention would need to result in an average weight loss of at least 2.5 kg at the end of 12 weeks in order to be considered meaningful. Under the assumption that the standard deviation of weight change would be similar to that seen in our previous study (3.5 kg),³² it was determined that a sample-size of 20 participants would provide statistical power of 90% (one-tailed, $\alpha = 0.05$) to detect a meaningful decrease in weight (i.e. 2.5 kg decrease).

Results

Participant characteristics are reported in Table 1. The average age was 54 years. The current activity level was reported as extremely inactive, sedentary, moderately active and vigorously active for 1 (5%), 2 (10%), 15 (75%), and 2 (10%) participants respectively. Of the 20 participants, 18 (90%) completed the medication phase and 2 (10%) discontinued study participation during the 12 week treatment phase (because of adverse event [headache]).

Weight, WC, and BMI at baseline, 6, 12 and 24 weeks are summarized in Table 2. The average weight at week 6 and week 12 was significantly ($p < 0.001$) decreased from baseline, with an average change of -1.9 kg (90% CI -2.5 to -1.2) at week 6 and -2.4 kg (90% CI -3.2 to -1.7) at week 12. At week 24, the average change in weight from baseline was not statistically significant (-0.7 kg, 90% CI -1.6 to $+0.2$ kg, $p = 0.09$). BMI followed a similar pattern. The average change from baseline was -0.7 kg/m² (90% CI -0.9 to -0.4) at week 6 and -0.9 (90% CI -1.2 to -0.6) at week 12. Inbody measurements are shown in Table 3 and display similar patterns to those seen with weight and BMI. Body fat mass and skeletal muscle mass were significantly decreased from baseline at weeks 6 and 12, but not week 24.

The VMS measurements of interest were the overall number of self-reported hot flashes and the number of hot flashes judged to be severe or very severe. At weeks 6 and 12 the overall number of hot flashes was significantly decreased from baseline, as was the number of severe/very severe hot flashes (Table 4). Additionally, the reduction in the number of hot flashes was seen within 2 weeks after initiating lorcaserin. The number of hot flashes (overall and those judged to be severe/very severe) increased within a week after lorcaserin was discontinued (Table 4 and Figure 3).

The participants did not experience any significant changes in their sexual function, sleep quality, depressive symptoms or quality of life during the study period (data not shown). Two participants withdrew from the study due to headache. One of the participants experienced a few seizure-like episodes 2 days after stopping the medication. These episodes

(a total of 8) lasted for 4 days, and resolved spontaneously. Similar adverse events have not been previously reported with lorcaserin discontinuation. The study team reported this occurrence as a serious adverse event. No other adverse events were noted to be related to the use of the study medication.

Discussion

The results of this pilot study show that the 5-HT_{2C} receptor agonist, lorcaserin, significantly reduced weight at 12 weeks from baseline in 20 overweight midlife women. The weight loss-inducing properties of lorcaserin are well recognized from four large prospective randomized controlled trials, and the medication was FDA-approved for this indication in 2012.^{33–36} However, to our knowledge, this is the first report that demonstrates that the 5-HT_{2C} receptor agonist may have a beneficial effect in menopausal VMS. This hypothesis could, however, not be tested in a randomized controlled trial. In February 2020, several months after completion of the current pilot study, the US FDA recommended that lorcaserin be withdrawn from the market due to a concern regarding increased risk of cancer.³⁷ This recommendation was based on the results of a single postmarketing study, conducted in roughly 12,000 patients, that found a marginally higher risk of cancer in those taking the medication compared with those who received placebo over a 5-year follow-up period (7.7% vs. 7.1%, respectively).³⁸ Prior to this study, there had not been any concerns regarding the safety of long-term lorcaserin use. Also, as with our current study, the medication had been reported to be generally well tolerated.²⁷ While this particular drug is no longer available in the US, the remarkable improvement in subjectively reported VMS observed with this 5-HT_{2C} receptor agonist in the current pilot study warrants further discussion regarding the potential mechanism(s) linking VMS and the 5-HT_{2C} receptor.

The pathophysiology underlying VMS has yet to be entirely elucidated. Recent evidence suggests that VMS are not triggered by an increase in core body temperature, but instead may be triggered by thermoregulatory mechanisms resulting in a transient decrease in the core temperature threshold for sweating or may be related to nonthermoregulatory mechanisms altogether.³⁹ Marked hypertrophic changes in the hypothalamic KNDy (kisspeptin, neurokinin B and dynorphin) neuronal pathways have been noted in postmortem studies of postmenopausal women, and based on preliminary data in an animal model, these pathways may be involved in hot flash generation.⁴⁰ Potential shared neural pathways between VMS and energy homeostasis support biological plausibility for a dual effect of the 5-HT_{2C} receptor on VMS and weight. Evidence suggesting that orexigenic pathways involving neuropeptide Y must be intact for normal function of kisspeptin neurons supports an association between kisspeptin and orexinergic hypothalamic neural networks.⁴¹ Although the exact mechanism of action of lorcaserin is unknown, it may be mediated by hypothalamic activation of anorexigenic pro-opiomelanocortin (POMC) neurons.⁴² Further support of a link between orexigenic neurons and VMS may be provided by a clinical trial investigating suvorexant, a dual orexin receptor antagonist that is FDA approved for treatment of insomnia, in the management of hot flash-associated insomnia (NCT03034018). Potential shared hypothalamic neuronal pathways involving VMS, energy homeostasis, and possibly sleep require further investigation.

While the current research findings are promising, it is important to acknowledge the significant placebo effect with use of medications to manage VMS.⁴³ Moreover, weight loss itself can improve VMS in recently postmenopausal women.^{44–46} However, it is important to note that in our study, the improvement in VMS occurred very rapidly, within 2 weeks of initiating therapy, well before the medication-induced weight loss occurred. Also, VMS returned rapidly after drug discontinuation, long before rebound weight gain occurred. Therefore, the improvement in VMS cannot be entirely explained by the weight loss. Moreover, we restricted our study population to overweight women, and excluded women with a BMI ≥ 30 kg/m² in order to avoid the effect of more dramatic weight loss on VMS as might have been seen in the obese women. Also, since lorcaserin was not approved for use in normal weight individuals, they were also excluded in the current pilot study. While the findings from this study should ideally be confirmed in a randomized placebo-controlled trial, recruiting both normal weight and overweight/obese women, this is not currently feasible due to lack of drug availability.

The findings from the current study advance our understanding of the pathophysiology and management of VMS. The serotonin 2C receptor may have a role (direct or indirect) in the pathophysiology of VMS, and this should be considered in future research evaluating nonhormone treatment strategies for VMS. MHT remains the most effective treatment for VMS,^{11,12,47} but many women either choose not to use or cannot use MHT due to contraindications. In such situations, women and their providers may turn to nonhormone pharmacotherapeutic options for management of VMS, including SSRIs, SNRIs, gabapentinoids, clonidine and oxybutynin.^{12–14,17} However, none of these medications promote weight loss, and some SSRIs and gabapentin may even lead to weight gain. There are also other potential adverse effects of therapy, including sexual dysfunction associated with SSRI and SNRI use.^{16,18,19,48} Conversely, the 5-HT_{2C} receptor agonist, lorcaserin, appears to have a dual effect of weight loss and reduction in VMS, and in this pilot study was not found to adversely impact sleep, sexual function or mood.

Conclusion

The selective serotonin 2C receptor agonist, lorcaserin, may have a beneficial effect on menopausal VMS in addition to its weight loss-inducing properties. However, the drug was withdrawn from the US market in February 2020 due to a slight increase in the risk of cancer in a single postmarketing study. The potential role of the 5-HT_{2C} receptor in VMS should be considered in future research investigating nonhormonal strategies for management of VMS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:
Flowchart of the study cohort

Figure 2:
Study Timeline

a

b.

Figure 3:
Trends in average daily hot flashes (top) and body weight (bottom) over 12-week treatment with lorcaserin.

Table 1:**Participant Characteristics**

<i>Participant Characteristics</i>	<i>(n=20)</i>
Age	
Mean $\pm$ SD	53.8 $\pm$ 3.1
Min, Max	48, 58
Marital status	
Never married	0 (0)
Separated/Divorced	0 (0)
Married	20 (100)
Race/Ethnicity	
White, Not Hispanic or Latino	20 (100)
Other	0 (0)
Education	
Some college	7 (35)
4-year college degree	9 (45)
Graduate/professional degree	4 (20)
Tobacco use	
Never	17 (85)
Former	3 (15)
Current	0 (0)
Alcohol use	
Never	2 (10)
Less than 1-2 drinks per week	9 (45)
1-2 drinks per week	3 (15)
3-5 drinks per week	4 (20)
5 or more times a week	2 (10)
Current Activity Level	
Extremely inactive	1 (5)
Sedentary	2 (10)
Moderately active	15 (75)
Vigorously active	2 (10)
Extremely active	0 (0)
Previous weight loss method attempts n (%)	
Tried on own without any aids	15 (75)
Counseling (group or individual)	4 (20)
Diet	13 (65)
Surgery	2 (10)
Other methods (e.g. exercise)	4 (20)

SD: standard deviation

Table 2:

Weight changes with lorcaserin use

	<i>Weight (kg) (n=18)</i>	<i>Waist Circumference (n=18)</i>	<i>BMI (n=18)</i>
Baseline			
Mean $\pm$ SD	80.9 $\pm$ 5.4	93.2 $\pm$ 5.9	29.7 $\pm$ 1.2
Week 6			
Mean $\pm$ SD	79.1 $\pm$ 5.4	92.6 $\pm$ 7.0	29.0 $\pm$ 1.1
from baseline	-1.9 $\pm$ 1.6	-0.7 $\pm$ 3.4	-0.7 $\pm$ 0.6
(CI 90%), p-value ^A	(-2.5, -1.2), <0.001	(-2.0, 0.7), 0.21	(-0.9, -0.4), <0.001
Week 12^B			
Mean $\pm$ SD	78.5 $\pm$ 5.8	91.6 $\pm$ 5.3	28.8 $\pm$ 1.1
from baseline	-2.4 $\pm$ 1.9	-0.9 $\pm$ 3.5	-0.9 $\pm$ 0.7
(CI 90%), p-value ^A	(-3.2, -1.7), <0.001	(-2.4, 0.6), 0.16	(-1.2, -0.6), <0.001
Week 24^B			
Mean $\pm$ SD	80.6 $\pm$ 6.0	95.2 $\pm$ 6.1	29.5 $\pm$ 1.0
from baseline	-0.7 $\pm$ 2.1	1.3 $\pm$ 4.2	-0.4 $\pm$ 0.8
(CI 90%), p-value ^A	(-1.6, 0.2), 0.09	(-0.5, 3.0), 0.89	(-0.7, 0.0), 0.05

^AOne tailed, paired t-test with 90% confidence interval^BOne participant did not have data for this time point

BMI: body mass index; SD: standard deviation

Table 3:

InBody measurements

	<i>Body Fat Mass (n=18)</i>	<i>Skeletal Muscle Mass (n=18)</i>	<i>Percent Body Fat (n=18)</i>	<i>Visceral Fat Level (n=18)</i>
Baseline				
Mean ± SD	33.8 ± 3.4	25.7 ± 3.2	41.8 ± 4.3	17.0 ± 2.1
Week 6				
Mean ± SD	32.9 ± 3.2	25.1 ± 2.9	41.7 ± 4.0	16.6 ± 2.0
from baseline	-0.8 ± 1.2	-0.6 ± 0.8	-0.1 ± 1.4	-0.4 ± 0.7
(CI 95%), p-value ^A	(-1.5, -0.2), 0.01	(-1.0, -0.2), 0.01	(-0.8, 0.6), 0.73	(-0.7, 0.0), 0.03
Week 12^B				
Mean ± SD	32.3 ± 3.5	25.2 ± 3.2	41.3 ± 4.4	16.5 ± 2.3
from baseline	-1.3 ± 2.1	-0.7 ± 1.0	-0.4 ± 2.0	-0.5 ± 1.1
(CI 95%), p-value ^A	(-2.4, -0.2), 0.02	(-1.2, -0.2), 0.01	(-1.4, 0.7), 0.45	(-1.0, 0.1), 0.09
Week 24^B				
Mean ± SD	33.5 ± 3.1	25.7 ± 3.1	41.2 ± 4.3	16.8 ± 2.0
from baseline	-0.4 ± 2.0	-0.1 ± 0.8	-0.7 ± 2.9	-0.3 ± 1.1
(CI 95%), p-value ^A	(-1.4, 0.6), 0.39	(-0.5, 0.3), 0.55	(-2.2, 0.8), 0.34	(-0.9, 0.3), 0.29

^A Paired t-test^B One participant did not complete visit

SD: standard deviation

Table 4:

Daily average number of hot flashes by week

	<i>Any HF (n=18)</i>	<i>Severe to Very Severe HF (n=18)</i>
Baseline		
Mean $\pm$ SD	7.3 $\pm$ 6.4	1.8 $\pm$ 3.1
Median (25, 75)	5.2 (4.5, 7.9)	1.00 (0, 1.5)
Week 6		
Mean $\pm$ SD	2.2 $\pm$ 3.6	0.5 $\pm$ 1.4
Median (25, 75)	0.6 (0.2, 2.7)	0.0 (0, 0)
from baseline	-5.2 $\pm$ 3.5	-1.3 $\pm$ 2.1
(CI 95%), p-value ^A	(-6.9, -3.5), <0.001	(-2.4, -0.3), 0.02
Week 12		
Mean $\pm$ SD	2.0 $\pm$ 3.2	0.4 $\pm$ 1.1
Median (25, 75)	0.9 (0.1, 2.1)	0.0 (0, 0)
from baseline	-5.4 $\pm$ 3.9	-1.4 $\pm$ 2.5
(CI 95%), p-value ^A	(-7.3, -3.4), <0.001	(-2.7, -0.2), 0.03
Week 13		
Mean $\pm$ SD	5.2 $\pm$ 9.6	1.7 $\pm$ 5.0
Median (25, 75)	2.8 (0.5, 5.1)	0.0 (0, 0)
from baseline	-2.2 $\pm$ 4.2	-0.1 $\pm$ 3.0
(CI 95%), p-value ^A	(-4.3, -0.1), 0.05	(-1.6, 1.4), 0.89

^A Paired t-test

HF: hot flash(es); SD: standard deviation