Effect of ArginMax on sexual functioning and quality of life among female cancer survivors: results of the WFU CCOP Research Base Protocol 97106

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Background Problems with sexual functioning are common following therapy for breast and gynecologic cancers, although there are few effective treatments.
Objective To assess the impact of ArginMax, a nutritional supplement comprised of extracts of L-arginine, ginseng, gingko, and damiana, as well as multivitamins and minerals, on sexual functioning and quality of life in female cancer survivors.
Methods This was a 12-week, randomized, placebo-controlled trial of eligible patients who were 6 months or more from active treatment and reporting problems with sexual interest, satisfaction, and functioning after therapy. The participants took 3 capsules of Arginmax or placebo twice daily. Outcome measures were the Female Sexual Function Inventory (FSFI) and the Functional Assessment of Cancer Therapy - General (FACT-G). Assessments were done at baseline, 4, 8, and 12 weeks.
Results 186 patients with a median age of 50 years were accrued between May 10, 2007 and March 24, 2010. 76% of the patients were non-Hispanic white. Most had breast or a gynecologic cancer (78% and 12%, respectively). At 12 weeks, there were no differences between the ArginMax group (n = 96) and placebo (n = 92) group in sexual desire, arousal, lubrication, orgasm, satisfaction or pain. However, FACT-G total scores were significantly better for participants who took ArginMax compared with those who took placebo (least squares [LS] means, 87.5 vs 82.9, respectively; $P = .009$). The Fact-G subscales that were most affected were Physical (25.37 vs. 23.51, $P = .001$) and Functional Well-Being (22.46 vs. 20.72, $P = .007$). Toxicities were similar for both groups.
Limitations Study results are limited by a lack of data on the participants' psychological and physical symptoms and sexual partner variables.
Conclusions ArginMax had no significant impact on sexual functioning, but patient quality of life was significantly better at 12 weeks in participants who received ArginMax.
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Sexual problems and dysfunction are common after therapy for breast and gynecologic malignancies.[1-9] Commonly reported problems are difficulties with arousal and orgasm, decreased sexual desire and sexual satisfaction, and psychological effects related to an altered body image and partner factors.[4-6,8] Jensen et al reported persistent sexual dysfunction and adverse vaginal changes after radiation for cervical cancer.[10] Prevalence rates for sexual problems vary by cancer type and treatment modality, but

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often affect 50% or more of all female cancer patients.[11-13]

Despite the recognized prevalence of sexual problems in survivors, there are relatively few studies that address interventions for women who have sexual complaints following cancer therapy.[14] One randomized, placebo-controlled study used a nutritional supplement, ArginMax, to treat sexual arousal disorder in healthy women without a history of cancer.[15-16] After 4 weeks of therapy, the women who received the supplement reported significant improvement in sexual desire and satisfaction compared with those in the placebo arm. ArginMax consists of extracts of L-arginine, ginseng, ginkgo, and damiana as well as multivitamins and minerals. Nitrous oxide is a byproduct of L-arginine metabolism and results in nitric oxide production, which triggers signaling pathways that lead to vasodilatation. Arginine is believed to be required to carry out the synthesis of nitric oxide that relaxes blood vessels and allows more blood to flow through arteries. Improving hemodynamics and genital blood flow may improve sexual response in women, as well as orgasmic and clitoral sensations.[17]

Given the positive results of this study and the relative lack of medical therapies for female patients with sexual dysfunction, we designed a placebo-controlled clinical trial to evaluate the use of ArginMax in female cancer survivors. We hypothesized that treatment with the supplement would improve the overall sexual functioning of study participants.

Methods

Eligibility and exclusions

This trial was designed and completed by the Community Clinical Oncology Program (CCOP) of the Comprehensive Cancer Center of Wake Forest University (CCCWFU) Research Base in Winston-Salem, North Carolina, and its affiliated community oncology member sites. The protocol was approved by the internal review board at the Wake Forest University Medical School. Participating WFU CCOP member sites were required to obtain IRB approval at their home institutions before opening the trial for recruitment at their respective sites.

Study participants were identified and recruited at WFU CCOP member sites from the rosters of diagnosed and treated patients. The main IRB inclusion criteria were female cancer survivors with sexual complaints who were at least 6 months post treatment, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. Current hormonal therapy and treatment with trastuzumab were allowed. Patients could have no evidence of active cancer, based on physical exam and radiographic images obtained within 2 months of study recruitment. In addition, patients could not have any disorder known to affect sexual function or be participating in another study with an investigational study drug or device during the 30 days before the start of the study drug. Laboratory values had to meet the following criteria at study entry to be able to identify laboratory abnormalities resulting from the study drug: hemoglobin, >10gm/dL; creatinine, <1.7; absolute neutrophil count, >1,500; platelets, >100,000; total bilirubin, <1.5. Study exclusions included: pregnancy; allergy to any compounds in ArginMax; current medications, specifically anticoagulants, antidepressants, clonidine, alpha blockers, or ginkgo biloba; uncontrolled intercurrent illness; or planned surgery or pregnancy during the study period.

During screening for study participation, survivors provided self-reported responses to 3 Yes or No questions about their current sexual complaints: whether they were dissatisfied with their sexual quality of life, whether they had problems with sexual arousal or fulfillment, and whether they had an interest in improving their sex life. Participants who answered Yes to all 3 questions and who met the aforementioned inclusion criteria, were asked to participate in this study. Participants who agreed to enroll in the study signed the IRB-approved informed consent and authorization forms before study registration and randomization were initiated and completed.

Randomization

The participants were stratified by type of malignancy (pelvic vs nonpelvic) and ovarian functional status (yes vs no) and randomized within strata to receive ArginMax or placebo with equal probability. Variable length permuted-block randomization was used to ensure approximately equal accrual to each treatment arm throughout the study. Block sizes of varying length were determined randomly to make it difficult for clinical staff to predict future assignments from past assignments. Treatment assignments were generated using Proc Plan in SAS and incorporated into the randomization table in the CCCWFU CCOP Research Base registration facility.

Treatment plan

Oral ArginMax or matching placebo was provided to patients free of charge by The Daily Wellness Company, Honolulu, HI. The study drug was independently analyzed for ingredients before it was distributed. All of the patients were instructed to take 3 caplets in the morning and 3 caplets in the evening each day and to complete a pill diary recording the number of pills taken daily. Sexual function, quality of life, and toxicity information were assessed at study baseline, before study pill initiation, and at clinic visits at 4, 8, and 12 weeks.

At study initiation, participants were provided with a 4-week supply of either Arginmax or placebo in 1 bottle. At 4 weeks, 2 more bottles of either ArginMax or placebo

were mailed directly to the participants by Biologics, Raleigh, NC, an independent company contracted by the WFU CCOP Research Base to distribute the final 8-week supply. Bottle lid labels with color-coded stickers were used entitled: Bottle 1, Bottle 2, and Bottle 3. Each bottle contained 168 caplets and was labelled with the participant's name.

Outcome measures

The primary outcome measure for this study was the Female Sexual Function Index (FSFI).[18-19] This measure was originally developed for patients with diagnoses of sexual disorders, such as hypoactive sexual desire or sexual arousal disorder, but has since been used with patients with chronic conditions, such as diabetes and cancer.[20] It has established reliability, validity, and sensitivity.[18-20] The FSFI is comprised of 6 subscales: sexual desire (2 questions), arousal (4), lubrication (4), orgasm (3), satisfaction (3), and pain (3). Subscale scores range from 1.2-6 (desire), 0-6 (arousal, lubrication, orgasm, and pain), and 0.8-6 (satisfaction). A total FSFI score is computed as the sum of the individual subscales; the overall score range is 2-36. A score of less than 26 on the total FSFI is an indication of sexual dysfunction.[20] Higher scores on both the total FSFI and subscales indicate better sexual functioning.

Health-related quality of life (HRQL), the secondary outcome measure, was assessed by the Functional Assessment of Cancer Therapy - General (FACT-G) questionnaire.[21] The FACT-G is comprised of 4 subscales that assess Physical Well-Being (7 items), Social Well-Being (7), Emotional Well-Being (6), and Functional Well-Being (7). A total FACT-G score is computed as the sum of the individual subscales; the overall score range is 0-108. Higher scores indicate better quality of life. The FACT-G has documented reliability and validity.[21]

Statistical considerations

The objectives of this randomized trial were to assess the effect of ArginMax on sexual function (primary outcome) and HRQL (secondary outcome) in female cancer survivors after 12 weeks of therapy. The study was powered to detect a 3.75 unit difference (an anticipated 15% relative difference) in the FSFI total score between the 2 groups with 90% power at the 5% two-sided level of significance, assuming a standard deviation for the FSFI of 6.0 and a dropout rate of 20%. The required sample size was 72 patients per group. Additional minority patients were recruited because of the low number of minority accruals during the original recruitment period (June 28, 2007-January 25, 2008), which brought the total sample size of recruited patients to 186.

Chi-square, Fisher exact, and Wilcoxon rank-sum tests were used to assess baseline group differences in categorical and continuous variables. A mixed effects repeated measures analysis of variance (RMANOVA) was used to assess treatment differences in sexual function and HRQL and to obtain least squares (LS) estimates of the measures over time. Models were constrained to have equal group means at baseline as proposed by Fitzgerald et al.[22] Additional mixed effects repeated measures analysis of covariance models were used to assess the impact of the participant baseline covariates on the changes in sexual function and HRQL.

Various covariance structures were considered for each model, including unstructured, compound symmetry, autoregressive, and toeplitz. The Bayesian information criterion was used to choose the most appropriate covariance structure for each outcome. Unadjusted models included only treatment group and time, while separate adjusted models also included the following covariates: age (in years), race (non-Hispanic white vs other), body-mass index (BMI), time since diagnosis (in months), primary cancer (breast, gynecologic, other), ovarian function (Yes/No), and 5 measures of sex/relationship quality at baseline – extent of sexual interest (moderate to extremely uninterested vs other), overall sexual satisfaction (moderately to extremely unsatisfied vs other), nonsexual relationship satisfaction (less than excellent vs excellent), frequency of intercourse (≤1 time/month vs >1 time/month), and frequency of climax (never/occasionally vs usually /always). The primary interest was in the effect of ArginMax at 12 weeks, and this effect was assessed by using a linear contrast within the repeated measures models. We also assessed the effect of the supplement on the average difference in the outcome measures over the 3 time points. Toxicities were documented using National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0 criteria.

Results

Recruitment and retention

One hundred eighty-six patients were accrued between June 28, 2007 and March 24, 2010. Initially, 145 women were accrued between June 28, 2007 and January 25, 2008 for an accrual rate of about 21 patients a month. Because of a lower-than-desired accrual of minority women, the recruitment period was extended for minority participants only, and an additional 41 minority women were recruited between April 21, 2008 and March 24, 2010, for an accrual rate of about 2 minority patients a month.

Overall, 74% of the participants completed the Week 12 visit (the time of primary interest), fewer than the 80% anticipated; 13% dropped out between baseline and the Week 4 visit, an additional 7% dropped out between weeks 4 and 8, and another 4% between weeks 8 and 12. Retention did not differ significantly between treatment

groups (P = .731). Most patients who dropped out (28 of 48; 58%) refused further treatment (15 patients) or were lost to follow-up (13 patients). Nine patients (19%) were removed because of toxicities. One patient had cancer progression (2%), 2 patients (4%) were advised to quit by their physicians, 3 (6%) had surgery, and 5 (10%) quit for other reasons. A total of 163 patients completed and returned their pill diaries. The median number of days completed was 83. The mean percent ideal dose (calculated as the percent of the ideal number of pills taken for recorded days) was 92.6 for the placebo group and 92.9 for the ArginMax group (P = .837). Assuming the worst (that no pills were taken on days that were not recorded), the percentage of the maximum ideal dose (assuming everyone stayed on study for 3 months) in the 2 groups would be 65.1 and 64.9, respectively (P = .928).

Baseline participant characteristics

Baseline characteristics of recruited participants are summarized in Table 1. Patient characteristics did not differ significantly between the treatment groups. The median age of the participants was about 50 years (range, 23-72). Primary cancer diagnoses were breast (78%); gynecologic (12%), and other (10%) The average time from cancer diagnosis was 41 months (range, 9-201). About 76% of the participants were non-Hispanic white, 21% were African-American, and 3% were Hispanic.

TABLE 1 Patient characteristics

Characteristic	Placebo (n = 92)	ArginMax (n = 94)	P
Age, y			.239
Median (range)	49 (23-71)	51 (28-72)	
≥50	45 (49)	55 (59)	
Median time since diagnosis, mo. (range)	40.8 (9-201)	41.4 (11-200)	.691
Body-mass index, kg/m^2			.487
Median (range)	29.3 (17.6-49.7)	27.9 (19.6-57.7)	
Underweight-normal [<25], n (%)	30 (33)	29 (31)	
Overweight [25-30], n (%)	19 (21)	29 (31)	
Obese [>30), n (%)	43 (47)	36 (38)	
Strata			—
Pelvic malignancy, OF	1 (1)	2 (2)	
Pelvic malignancy, no OF	9 (10)	10 (11)	
Not pelvic malignancy, OF	18 (20)	18 (19)	
Not pelvic malignancy, no OF	64 (70)	64 (68)	
Race/ethnicity			.230
White	69 (75)	72 (77)	
Black	18 (20)	21 (22)	
Hispanic	5 (5)	1 (1)	
ECOG-PS			.218
0	84 (91)	90 (96)	
1	8 (9)	4 (4)	
Primary tumor			.173
Colorectal	2 (2)	1 (1)	
Lung	1 (1)	1 (1)	
Breast	69 (75)	77 (82)	
Gynecologic	10 (11)	12 (13)	
Hodgkin	5 (5)	0 (0)	
Lymphoma	0 (0)	1 (1)	
Lymphoid tissue	1 (1)	0 (0)	
Multiple myeloma	1 (1)	0 (0)	
Leukemia	3 (3)	1 (1)	
Thyroid	0 (0)	1 (1)	

ECOG-PS, Eastern Cooperative Oncology Group - Performance Status; OF, ovarian function

Baseline sexual functioning

At baseline, patients were asked on a scale of 1-5 to describe the extent of their sexual interest, their overall sexual satisfaction, and their satisfaction in their relationship (excluding intercourse). Participants were also asked to quantify their intercourse and orgasm frequency. The responses to these items did not differ significantly between the 2 treatment groups (Table 2). About 58% of the ArginMax group and 53% of the placebo group reported that they had had sexual intercourse <1 time in the previous month; 22% of the ArginMax group and 25% of the placebo group reported that they generally never achieved sexual climax. Two-thirds of the participants reported that they were either unsatisfied or extremely unsatisfied sexually, with a roughly equivalent proportion indicating that they were uninterested or extremely uninterested in sex. However, despite the problems and dissatisfaction with their sexual functioning, most of the women rated their relationship with their significant other (excluding intercourse) as very good to excellent.

Outcomes

Primary – sexual functioning. Least squares (LS) means for the FSFI scores based on the unadjusted constrained models are summarized in Table 3 by treatment arm and time point. Higher scores indicate better sexual functioning. At baseline, sexual functioning was low with a total FSFI LS mean (standard error [SE]) of 14.1 (0.6), less than half the maximum score possible and well below the cutoff score of 26. The total FSFI scores did increase significantly from baseline to 4 weeks in both groups (P < .001), but the increases were similar in the ArginMax and placebo groups and all scores were still below 26, which suggested a high degree of sexual problems among these participants.

Mixed effects repeated measures analysis of covariance models were run to assess the effects of the covariates on the change in FSFI and to assess the effect of treatment after adjustment for covariates. These models demonstrated basically the same results as the constrained models for treatment group, and conclusions are identical for both the unadjusted and adjusted models. ArginMax had no significant effect on the overall FSFI score or on any subscale. There were also no significant interactions between treatment group and the baseline sexual functioning measures, meaning that the treatment effect did not differ significantly by the starting level of sexual functioning. Improvements in the total FSFI and the subscale scores during the course of the study were largely associated with younger participants, those with greater sexual interest, and those having more frequent intercourse.

Separate models were run for the FSFI total score and each subscale score that included an interaction between race and treatment. Those interactions were not statistically significant for any sexual function outcome, meaning that the effect of treatment did not differ significantly by race. However, our study was not powered to detect interactions, so separate models were run for non-Hispanic whites and for all racial/ethnic minorities combined. Only unadjusted models were run because the unadjusted and adjusted models gave the same results as in the entire cohort and because the number of minority patients did not readily support a large adjusted model. The effect of ArginMax was similar for non-Hispanic whites and minorities for all the sexual function measures, and no significant differences were found by race/ethnicity.

Secondary – health-related quality of life. LS means for the FACT-G total and subscale scores, based on the unadjusted, constrained models, are summarized in Table 4 by treatment arm and time. Higher scores indicate better HRQL. At baseline, the LS mean (SE) for the total FACT-G score was 87.0 (1.01), with a range of 29-106. At 12 weeks, the pre-specified time point of interest, the total FACT score ($P = .010$), the Physical Well-Being ($P = .001$), and the Functional Well-Being ($P = .007$) subscales differed significantly in favor of ArginMax. Averaged across the 3 time points, the total FACT score ($P = .017$), and the Physical ($P < .001$) and Emotional ($P = .030$) subscales differed significantly by treatment group.

To further explore these differences, mixed effects repeated measures analysis of covariance models were run to assess the effects of the covariates (demographic and clinical variables) on the change in FACT total and subscales scores after adjustment for covariates. These results (not shown) indicated that age was significantly associated with the change in the physical subscale (older patients had less improvement in physical functioning, $P = .001$), time from diagnosis was associated with the change in the social subscale (the longer the time since diagnosis the less the improvement in the participant's social functioning, $P = .028$), the extent of baseline sexual interest was associated with the change in the emotional subscale (those with more sexual interest had less improvement in emotional functioning, $P = .011$), and the frequency of intercourse was associated with the change in the functional subscale

TABLE 2 Sexual function and quality at baseline

Characteristic	Placebo (n = 92)	ArginMax (n = 94)	P
Extent of sexual interest			.835
1 Extremely uninterested	27 (30)	25 (27)	
2 Uninterested	31 (34)	35 (37)	
3 Neutral	17 (19)	14 (15)	
4 Interested	9 (10)	9 (10)	
5 Extremely interested	7 (8)	11 (12)	
Overall sexual satisfaction			.645
1 Extremely unsatisfied	27 (30)	23 (24)	
2 Unsatisfied	32 (36)	42 (45)	
3 Neutral	27 (30)	25 (27)	
4 Satisfied	4 (4)	4 (4)	
5 Extremely satisfied	0 (0)	0 (0)	
Satisfaction with relationship (excl. intercourse)			.437
1 No satisfaction	6 (7)	4 (4)	
2 Fair	7 (8)	7 (7)	
3 Good	19 (21)	11 (12)	
4 Very good	19 (21)	23 (24)	
5 Excellent	40 (44)	49 (52)	
Frequency of intercourse			.701
1 None	14 (15)	20 (21)	
2 ≤1 time/mo.	35 (38)	35 (37)	
3 >1 time/ mo. but < 3 times/wk	40 (44)	36 (38)	
4 >3 times/wk	2 (2)	3 (3)	
Frequency of sexual climax			.577
1 Never	23 (25)	20 (22)	
2 Occasionally	43 (47)	49 (53)	
3 Usually	22 (24)	18 (19)	
4 Always	3 (3)	6 (6)	

TABLE 3 Least squares estimates of the Female Sexual Function Inventory total and subscale scores by group and time

Outcome	Week	Placebo, mean (SE)	ArginMax, mean (SE)	*P*	
				Average	Time specific
Total FSFI				.827	
	0	14.15 (0.62)	14.15 (0.62)		–
	4	17.40 (0.80)	16.66 (0.80)		.433
	8	17.55 (0.84)	17.07 (0.85)		.642
	12	17.15 (0.91)	17.81 (0.90)		.576
Desire				.748	
	0	1.98 (0.08)	1.98 (0.08)		–
	4	2.34 (0.11)	2.34 (0.11)		.962
	8	2.50 (0.11)	2.41 (0.11)		.578
	12	2.33 (0.12)	2.53 (0.12)		.214
Arousal				.488	
	0	2.12 (0.11)	2.12 (0.11)		–
	4	2.67 (0.15)	2.60 (0.15)		.709
	8	2.55 (0.16)	2.77 (0.16)		.271
	12	2.61 (0.17)	2.78 (0.17)		.428
Lubrication				.230	
	0	2.27 (0.14)	2.27 (0.14)		–
	4	3.03 (0.18)	2.72 (0.18)		.145
	8	3.06 (0.19)	2.70 (0.19)		.151
	12	3.04 (0.21)	3.00 (0.20)		.894
Orgasm				.887	
	0	2.13 (0.14)	2.13 (0.14)		–
	4	2.63 (0.18)	2.43 (0.18)		.372
	8	2.69 (0.19)	2.63 (0.19)		.800
	12	2.62 (0.20)	2.80 (0.20)		.504
Satisfaction				.868	
	0	2.66 (0.11)	2.66 (0.11)		–
	4	3.20 (0.15)	2.91 (0.15)		.120
	8	3.12 (0.15)	3.03 (0.15)		.644
	12	3.04 (0.16)	3.35 (0.16)		.149
Pain				.422	
	0	2.98 (0.17)	2.98 (0.17)		–
	4	3.44 (0.23)	3.32 (0.22)		.671
	8	3.67 (0.24)	3.37 (0.24)		.305
	12	3.50 (0.25)	3.35 (0.25)		.647

(those having more frequent intercourse showed more functional improvement, $P = .009$). No covariates were significantly associated with the change in the total FACT-G score, however.

We also assessed the interaction between treatment group and baseline FACT-G total and subscale scores. For all FACT-G subscales, except the Functional Well-Being subscale, there was a significant interaction, meaning that the treatment effect was greater for those with lower FACT-G scores at baseline. Table 5 provides the LS means (SEs) for the total score of the FACT-G and the 4 subscales for models stratified by the baseline value of the particular measure. ArginMax had a 7.1-unit benefit in participants whose baseline FACT-G total scores were below 89 ($P = .014$) while having no effect in participants whose baseline FACT-G total scores were 89 or higher ($P = .942$). Similarly, ArginMax had a 2.1-unit benefit in physical functioning for those participants who scored below the median baseline physical functioning subscale score of 25 ($P = .009$), compared with a 0.8-unit benefit for those participants whose baseline scores were 25 or higher ($P = .050$).

Serious adverse events and toxicities

Five serious adverse events were reported, 3 on the ArginMax arm (grade 3 stomach pain followed by diarrhea, grade 3 night sweats and insomnia, and grade 3 abscess of the vulva) and 2 for the placebo arm (grade 3 hyperglycemia, grade 3 infection). Only the stomach pain and diarrhea was thought to be possibly related to treatment. Patients were also questioned at each visit about specific toxicities (headaches, hot flashes, nausea, neuropathy, and vomiting). Hot flashes were the most commonly reported event, occurring in 66% of the patients, and were severe for 3 patients in each arm. Headaches were the next most common toxicity, occurring in 29% of the patients. Neuropathy occurred in 19% of the patients, nausea in 9%, and vomiting in 3%. These toxicities did not differ significantly between groups.

Discussion

After 12 weeks of therapy, this trial demonstrated no benefit of ArginMax treatment for improving sexual functioning in this group of female cancer survivors. However, ArginMax therapy did result in improved HRQL, primarily in the physical and functional well-being domains. This improvement was greater for those with lower baseline FACT-G total and subscale scores.

It is difficult to ascertain why this improvement in HRQL occurred. It is plausible that this finding may be a result of improved systemic blood flow.[23-24] Increased

blood flow may have enhanced the participants' overall physical functioning and ability to perform desired work and family roles. There may also have been some psychological benefit to participating in the trial, particularly among those with lower FACT-G scores at baseline, in that the participants were taking steps to try to improve their sexual functioning, even if the end result was not as they had anticipated. Nevertheless, these quality of life findings are intriguing and warrant further investigation in future clinical trials.

Limitations to our study included a higher-than-expected dropout rate during the course of the study. We also had a lack of variables assessing psychological or physical symptoms (anxiety, depression, fatigue, sleep disturbance) experienced by the participants, as well as information on partner/relationship aspects that might have affected the participants' sexual functioning. In addition, we had no knowledge of the participants' sexual activity or problems before their diagnosis of cancer. The inclusion of more of these variables may have enabled a greater explanation of the study findings.

Strengths of the research were the randomized, controlled trial design, the documented clinical and treatment characteristics of the participants, as well as the resources of the WFU CCOP Research Base.

More research to find effective therapies for female sexual problems following cancer therapy is needed. Given the growing numbers of cancer survivors, emphasis on developing effective therapies for sexual concerns should be an imperative. Interventions combining effective medical therapies for sexual problems with psychological and/or couple aspects may achieve greater success in alleviating this health and quality of life concern.

TABLE 4 Least squares estimates of the Functional Assessment of Cancer Therapy - General total and subscale scores by group and time

Outcome	Week	Placebo, mean (SE)	ArginMax, mean (SE)	*P* Average	*P* Time specific
Total FACT-G				.017	
	0	87.03 (1.01)	87.03 (1.01)		—
	4	84.92 (1.21)	87.92 (1.21)		.017
	8	86.84 (1.27)	88.27 (1.29)		.325
	12	85.47 (1.39)	89.96 (1.38)		.010
Physical				<.001	
	0	23.32 (0.31)	23.32 (0.31)		—
	4	23.20 (0.39)	24.68 (0.39)		.002
	8	23.73 (0.41)	24.91 (0.41)		.020
	12	23.51 (0.43)	25.27 (0.42)		.001
Social				.566	
	0	21.50 (0.36)	21.50 (0.36)		—
	4	21.18 (0.44)	20.85 (0.44)		.481
	8	21.36 (0.46)	20.55 (0.47)		.134
	12	21.15 (0.48)	21.56 (0.48)		.475
Emotional				.030	
	0	20.11 (0.25)	20.11 (0.25)		—
	4	19.59 (0.33)	20.50 (0.33)		.022
	8	19.95 (0.35)	20.84 (0.35)		.046
	12	20.09 (0.38)	20.61 (0.37)		.294
Functional				.054	
	0	21.92 (0.39)	21.92 (0.39)		—
	4	20.87 (0.46)	21.73 (0.46)		.074
	8	21.72 (0.48)	21.77 (0.48)		.930
	12	20.72 (0.53)	22.46 (0.52)		.007

TABLE 5 Least squares means (SEs) for average treatment effects by baseline covariate level

Outcome, median	< Median: Placebo, mean (SE)	< Median: ArginMax, mean (SE)	< Median: *P*	> Median: Placebo, mean (SE)	> Median: ArginMax, mean (SE)	> Median: *P*
Total FACT-G, 89.0	74.1 (1.88)	81.2 (2.07)	.014	95.1 (0.90)	95.0 (0.84)	.942
Physical, 25.0	21.2 (0.62)	23.4 (0.55)	.009	25.6 (0.27)	26.4 (0.30)	.050
Social, 23.0	17.7 (0.61)	18.2 (0.58)	.573	24.0 (0.41)	23.2 (0.43)	.206
Emotional, 21.0	17.9 (0.50)	19.0 (0.49)	.125	21.5 (0.27)	21.9 (0.27)	.242
Functional, 23.0	18.1 (0.57)	18.7 (0.58)	.470	23.7 (0.43)	24.7 (0.42)	.123

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