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Evaluating the efficacy of vaginal dehydroepiandrosterone for vaginal symptoms in postmenopausal cancer survivors: NCCTG N10C1 (Alliance)

Debra L. Barton¹, Jeff A. Sloan², Lynne T. Shuster³, Paula Gill³, Patricia Griffin⁴, Kathleen Flynn⁵, Shelby A. Terstriep⁶, Fauzia N. Rana⁷, Travis Dockter², Pamela J. Atherton², Michaela Tsai⁸, Keren Sturtz⁹, Jacqueline M. Lafky³, Mike Riepl¹⁰, Jacqueline Thielen³, and Charles L. Loprinzi³

¹University of Michigan School of Nursing, Ann Arbor, MI

²Alliance Statistics and Data Center, Mayo Clinic, Rochester, MN

³Mayo Clinic, Rochester, MN

⁴Southeast Clinical Oncology Research (SCOR) Consortium NCORP, Spartanburg Medical Center, Spartanburg, SC

⁵Michigan Cancer Research Consortium NCORP, Ann Arbor MI

⁶Meritcare Hospital CCOP, Fargo, ND

⁷Mayo Clinic Florida, Jacksonville, FL

⁸Metro-Minnesota NCORP, St. Louis Park, MN

⁹Colorado Cancer Research NCORP, Denver, CO

¹⁰Gateway Pharmacy North, Bismarck, ND

Abstract

Background—Women with estrogen deficiencies can suffer from vaginal symptoms that negatively impact sexual health. This study evaluated vaginal dehydroepiandrosterone (DHEA) for alleviation of vaginal symptoms.

Methods—This three-arm randomized, controlled trial evaluated DHEA 3.25 mg and DHEA 6.5 mg, each compared to a plain moisturizer (PM) over 12 weeks, to improve the severity of vaginal dryness or dyspareunia, measured with an ordinal scale, and overall sexual health using the Female Sexual Function Index (FSFI). Postmenopausal women with a history of breast or gynecologic cancer who had completed primary treatment, had no evidence of disease, and reported at least moderate vaginal symptoms were eligible. The mean change from baseline to

Corresponding Author: Debra L. Barton RN, PhD, AOCN, FAAN, Mary Lou Willard French Professor of Oncology Nursing, University of Michigan School of Nursing, 400 N. Ingalls, Room 4304, Ann Arbor, MI 48109-5482, Phone: (734) 763-3868, Fax: (734) 647-2416, debbartn@med.umich.edu.

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week 12 in the severity of vaginal dryness or dyspareunia for each DHEA dose was compared to PM and analyzed by two independent t-tests using a Bonferroni correction.

Results—Four hundred sixty-four women were randomized. All arms reported improvement in either dryness or dyspareunia. Neither DHEA dose was statistically significantly different from PM at 12 weeks (6.25 mg, $p=.08$; 3.25 mg, $p=0.48$), although a significant difference at 8 weeks for 6.5 mg DHEA was observed ($p=0.005$). Women on the 6.5 mg arm of DHEA reported significantly better sexual health on the FSFI ($p<0.001$). There were no significant differences in provider-graded toxicities and few significant differences in self-reported side effects.

Conclusion—PM and DHEA improved vaginal symptoms at 12 weeks. However, vaginal DHEA, 6.5 mg, significantly improved sexual health. Vaginal DHEA warrants further investigation in women with a history of cancer.

Background

Prevalence and significance

Sexual health is considered a major survivorship issue worthy of attention that, to date, is not well addressed in cancer care^{1–3}. Women diagnosed with breast or gynecologic cancer can experience a decline in sexual health soon after diagnosis^{4–7} which may persist or worsen over five years⁵. The prevalence of sexual health issues has been estimated to be 30 to 100%^{6,7}.

One of the most consistently identified predictors of impaired sexual health in women is the presence of vaginal symptoms^{8–12}. The vagina is highly regulated by estrogen, therefore cancer treatment that results in estrogen depletion causes unwanted effects on the vagina resulting in vaginal dryness and discomfort, pain and bleeding associated with intercourse, and increased susceptibility to infections, all of which may impair enjoyment of sexual intimacy¹³.

Standard/current treatment

The gold standard treatment for vaginal symptoms is low dose vaginal estrogen^{14,15} (e.g., 7.5 micrograms [mcg] suppository) to provide symptom relief while minimizing systemic effects, but use in the breast oncology community is controversial, particularly for women on aromatase inhibitors (AI). A small group of retrospective studies have not demonstrated increased rates of breast cancer recurrence with the use of vaginal estrogens or oral estrogen therapy^{16–18}, but definitive safety studies are not currently available.

Recent ASCO/ACS survivorship guidelines and the North American Menopause Society recommend the use of non-hormonal treatments, specifically water- or silicone-based lubricants and vaginal moisturizers as first line treatment^{15,19}. Lubricants are used at the time of sexual activity. Vaginal moisturizers, involving bases such as polycarbophil, hyaluronic acid, gums or gelatins, may be used on a regular basis for hydrating vaginal tissue. Moisturizers have been shown to improve symptoms and pH, but have not been shown to improve tissue health, specifically cell maturation¹⁴.

Localized dehydroepiandrosterone (DHEA) has been evaluated as a treatment for vaginal dryness and dyspareunia and has demonstrated efficacy^{20–23}. A DHEA containing ovule has just been FDA approved for moderate to severe dyspareunia in postmenopausal women. DHEA is produced primarily by the adrenal gland and serves as a precursor to estrogen and androgen production. It has low androgenic potency. Previous work with DHEA has reported that, when administered vaginally, it is converted into active forms of estrogen and/or testosterone on intracellular receptors, providing local activity^{20,22}.

Vaginal DHEA has not been studied in women with a history of cancer, and given the extreme estrogen deprivation women on aromatase inhibitors experience, it is not possible to generalize results from studies in women with natural or surgically induced menopause to cancer survivors, particularly those on AI's. Therefore, in this study we sought to evaluate two low doses of vaginal DHEA 3.25 mg and 6.5 mg, to minimize the amount of drug exposure, for the symptoms of vaginal dryness or dyspareunia in female cancer survivors.

Methods

Eligibility

Women eligible for this study included those who were postmenopausal, with a history of breast or gynecologic cancer and no current evidence of disease who had completed chemotherapy and radiation. Women had to report either dyspareunia or vaginal dryness of at least moderate severity and this symptom had to have been present for at least two months.

Women could be on tamoxifen or an AI for at least 8 weeks, without plans to change treatment during the study. Participants could not use vaginal products other than water-based lubricants during intercourse. Women were not eligible for the study if they had prior pelvic surgery resulting in anatomical changes, had prior radiation to the pelvis, active vaginal infections, or had used any hormonal product (including soy or any compounded hormones) in the preceding 4 weeks.

Randomization

In this three-arm randomized controlled trial, women were randomized to receive either DHEA 3.25 mg or DHEA 6.5 mg in a bioadhesive moisturizer base or a plain bioadhesive moisturizer alone (PM). Both investigators and patients were blinded to treatment assignment. Randomization was accomplished using the Pocock-Simon dynamic allocation procedure that balances the marginal distributions of the stratification factors between the treatment groups²⁴. Women were stratified by hysterectomy status (yes or no), cigarette smoking history (current, past or never), use of AIs (anastrozole/letrozole, exemestane or none), and the current use of tamoxifen (yes or no).

Measures

The primary aim of this study was to compare DHEA 3.25 mg versus PM and DHEA 6.5 mg versus PM over 12 weeks for the alleviation of the most bothersome vaginal symptom. The primary endpoint was measured with an ordinal scale, where women rated severity of

their most bothersome symptom, either dryness or dyspareunia, as none, mild, moderate, severe or very severe. The choice of this primary outcome was influenced by two factors; this was the outcome used in the previous DHEA trial whose product is now FDA approved²¹ and both symptoms are well established sequelae of the effects of estrogen deprivation on the vagina^{13,15,25}. The primary outcome measure was administered at baseline and at weeks 2, 4, 8 and 12.

Secondary outcomes included side effects as measured by provider-reported Common Terminology Criteria of Adverse Events (CTCAE) v4.0 and an investigator-developed self-report questionnaire which asks participants to report on 8 potential toxicities and overall quality of life (QOL), using a numeric analogue scale from 0 (“not at all”) to 10 (“as bad as it can be”)²⁶. For the analysis, these numbers were inverted such that negative numbers indicate worsening of symptoms and positive numbers indicate improvement. Side effects were measured at baseline and weeks 2, 4, 8 and 12.

An important secondary outcome was overall sexual function, measured by the Female Sexual Function Index (FSFI)²⁷. The FSFI is a relatively brief multi-dimensional measure of 19 items that addresses the major domains of female sexual functioning, including desire, arousal, lubrication, orgasm, satisfaction, and pain. The FSFI has been validated for use in adult women, including cancer survivors²⁸, with the most recent Cronbach alphas being over 0.9 for internal reliability. A score of 26 is reported to be the cut point to distinguish women with and without sexual dysfunction (lower scores indicating sexual dysfunction)²⁹, other dysfunction scores are 3 in the pain subscale and 4.35 for the lubrication subscale²⁹. The FSFI was completed at baseline and 12 weeks.

Several physiologic endpoints were evaluated, including hormone concentrations and biomarkers of bone turnover, and are to be published separately.

Intervention and control

Vaginal DHEA was developed by a compounding pharmacist located in North Dakota. An IND, # 111454, was obtained. The base of the compound, developed specifically for this study to be bioadhesive, included carbomer, squalane, vitamin E acetate USP liquid, distilled water, methylparaben NF powder, propylparaben NF powder, glycerin and zinc acetate and was used as the plain moisturizer for the control arm of this study. The DHEA was added to result in either 3.25 mg/0.4 mL or 6.5 mg/0.4 mL gel. Small syringes without a needle, used as applicators, were prefilled with DHEA or plain moisturizer gel. All study syringes were identical in all respects so the assigned treatment was blinded. Study participants were instructed to insert one syringe of gel daily right before going to bed, after any sexual activity, in a ribbon like fashion, withdrawing the syringe slowly as they pushed the plunger to apply the gel. Women were asked to do this every night for 12 weeks.

Statistical analysis

Sample size was determined to balance the need for an appropriate effect size and results that were clinically meaningful³⁰. An effect size of 0.36 SD was selected for this trial to provide clinical relevancy and based on previous work by Labrie^{21,23}. Using a Bonferroni correction due to having two correlated primary hypothesis tests,³¹ 3.25 mg DHEA vs plain

moisturizer and 6.5 mg DHEA vs plain moisturizer, 145 patients per group were required to provide 80% power to detect a difference of 0.36 SD with a type I error of 2.5%.

The primary analysis considered the endpoint as continuous in nature and used the mean change from baseline to week 12 in the woman's most bothersome symptom, either dryness or dyspareunia. Two independent paired t-tests were utilized. The study results were confirmed using logistic regression when considering the endpoint as ordinal in nature and using the last value carried forward missing data imputation method. Finally, subset analyses were performed to look at potential AI effects on outcomes.

Summary statistics including means and frequencies were calculated, and endpoints analyzed with the appropriate statistical methods including chi-square tests, Fisher-exact tests, and t-tests.

This study was monitored by the NCCTG External Data Monitoring Committee (DMC), a National Cancer Institute-approved body, and registered NCT01376349. Reports containing efficacy, adverse event, and administrative information were provided to the DMC every six months per NCI guidelines. Each participant signed an IRB-approved informed consent in accordance with federal and institutional guidelines.

Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center (SDC). Data quality was ensured by review of data by the Alliance SDC and by the study chairperson (DLB) following Alliance policies. Analyses were based on the study database frozen on July 15, 2013.

Results

Accrual and demographics

The CONSORT diagram is shown in Figure 1. Eighty-two institutions across the United States and Canada enrolled 464 women between July, 2011 and April, 2013; 147–149 women were randomized to each arm. Attrition rates were 18% leaving 112–123 per arm with primary endpoint data. Baseline characteristics of the women in the study (Table 1) were not significantly different between arms. At baseline, the percentage of women reporting dryness as their most bothersome symptom was 49% in the PM group, 40% in the 3.25 mg DHEA arm, and 42% in the 6.5 mg DHEA group while those reporting dyspareunia as the most bothersome symptom were 51% in the PM group, 60% in the 3.25 mg DHEA group and 58% in the 6.5 mg DHEA arm. The mean severity of the most bothersome symptom (dryness or dyspareunia) was rated as 4 for women in each DHEA arm and 4.1 for women in the PM group (out of a possible 5) indicating it was severe.

Primary outcome

The change from baseline to week 12 for the most bothersome symptom decreased for all arms as follows: PM: -1.5 (CI: $-1.74, -1.27$), 3.25 mg DHEA: -1.6 (CI: $-1.79, -1.35$) and 6.5 mg DHEA: -1.8 (CI: $-1.97, -1.54$). These reductions were not significantly different between arms. Missing data imputation confirmed the non-significant primary results for the

3.25 mg DHEA vs. PM ($p=0.57$) and 6.5 mg DHEA dose vs. PM ($p=0.03$), using the Bonferroni corrected p -value.

Mean values over the 12 weeks of the study for all arms are shown in Figure 2. At week 8, there was a statistically significant decrease in the most bothersome symptom for women in the 6.5 mg vaginal DHEA arm compared to those in the PM arm ($p=0.005$), but this did not remain statistically significant at 12 weeks.

Secondary outcomes

There were no statistically significant differences between groups in any grade toxicity as graded by the CTCAE version 4.0 (data not shown). The most common clinician graded CTCAE side effects ($>5\%$) included headache and breast pain, which were not different between arms. Hirsutism and specific components of hirsutism (voice alteration, increased body hair and acne) were graded by providers primarily as grade 1 (98%) and, again, there were no significant differences between arms.

Self-reported side effect changes during the study are listed in Table 2. Small, but statistically significant, differences occurred in women receiving DHEA compared with PM, with worsening voice changes reported among women in the 3.25 mg and 6.5 mg DHEA arms, and headaches in the 3.25 mg DHEA arm compared to PM.

Mean values and change from baseline for the FSFI subscales of arousal, lubrication, satisfaction and pain as well as the total score (overall sexual function) for the FSFI and overall QOL are shown in Table 3. Overall sexual function and QOL improved significantly in the 6.5 mg DHEA group compared to the PM group ($p = 0.01$ for both FSFI total score and QOL). In addition, women receiving DHEA 6.5 mg reported significant improvements in all subscales of the FSFI (arousal, lubrication, pain, and satisfaction) with the exception of orgasm, compared to PM; while women receiving 3.25 mg of DHEA reported significant improvements on arousal and pain subscales compared to those receiving the PM.

Use of an AI, versus not, did not lead to any difference in the primary (most bothersome symptom of dryness or dyspareunia) or secondary (FSFI subscales or total score) outcomes. Within those women receiving DHEA, the change in severity for the most bothersome symptom at 12 weeks was -1.7 (CI: $-1.91, -1.48$) for those on an AI ($N=126$), and -1.6 (CI: $-1.85, -1.40$) for those not on an AI ($N=116$) ($p=0.76$). Similar benefits were demonstrated on the FSFI, the total score change at 12 weeks was 6.5 for women on an AI and 6.1 for women not on an AI ($p=0.47$).

In an exploratory manner, the severity of vaginal dryness and dyspareunia were analyzed separately. Patients scored the severity of dryness and severity of dyspareunia very similarly on all arms of the study. The change in baseline to week 12 in vaginal dryness was -1.3 (CI: $-1.56, -1.11$) for 3.25 mg DHEA, -1.5 (CI: $-1.70, -1.24$) for 6.5 mg DHEA and -1.4 (CI: $-1.60, -1.16$) for PM. The change in baseline to week 12 in dyspareunia was -1.3 (CI: $-1.52, -1.03$) for 3.25 mg DHEA, -1.5 (CI: $-1.78, -1.28$) for 6.5 DHEA mg and -1.4 (CI: $-1.61, -1.09$) for PM. No comparisons of any of these endpoints to PM were statistically significant, thus DHEA did not affect one symptom more than the other.

Discussion

The data from this randomized clinical trial demonstrates that over 12 weeks, a vaginal bioadhesive moisturizer and DHEA both improve the severity of vaginal symptoms of pain or dryness. DHEA 6.5 mg, however, improved symptoms more quickly, with a significant difference at 8 weeks. In addition, only women in the DHEA arms reported significant improvement on the sexual health measure. Thus, this study provides partial support and some consistency with previously published data on vaginal DHEA^{21,23}. Specifically, the data from this study demonstrates improved sexual function, as measured by the FSFI, with the use of DHEA. In fact, per well-established cut points for the pain subscale of the FSFI, as reported in Table 2, only women receiving DHEA reported post treatment mean scores in the normal range (≥ 3)²⁹. Further research could identify those women whose symptoms are not adequately managed with a plain bioadhesive moisturizer, who might benefit from DHEA.

It may seem surprising that a bioadhesive moisturizer over a 12-week period improved vaginal symptoms of dryness and dyspareunia. Current recommendations for the use of a moisturizer is 3 to 5 days per week. In our study, women used the moisturizer every night for 12 weeks. It may be that increased frequency is necessary for women with more moderate to severe vaginal symptoms to experience symptom improvement. This study provides data that supports that the use of a moisturizer over 12 weeks, used before bed after any sexual activity, was able to improve vaginal symptoms, no matter whether it was dryness or dyspareunia. We hypothesize that nightly application of the moisturizer was important to allow tissue hydration.

Based on the two self-reported side effects (voice change and headaches) that were statistically significantly worse than the plain moisturizer, it is important to note that some women may experience androgen related side effects on DHEA. As in all treatment for symptoms, individual risk/benefit should be evaluated. Physiologic endpoints for this study, including androgen concentrations, will be reported separately.

Recently, additional treatments have been found to be helpful in alleviating vaginal symptoms. One oral option, Ospemifene, is a Food and Drug Administration-approved selective estrogen receptor modifier (SERM) for moderate to severe dyspareunia in postmenopausal women. As a systemically active agent, this drug is associated with potential adverse effects including hot flashes and venous thromboembolic events¹⁵, and has not been studied in women with breast or gynecologic malignancies. Another treatment, topical 4% lidocaine, was recently shown to improve pain and/or tenderness in the vulvar vestibule³². This small study recruited women shown to positively respond to topical lidocaine, and then evaluated the treatment in a randomized, blinded trial. Therefore, this treatment option is specific to vulvar issues and is not likely to improve more general symptoms in the vaginal vault.

In summary, daily use of a vaginal moisturizer has the ability to improve vaginal symptoms over 12 weeks but may not sufficiently positively impact overall sexual function. For that

reason, the role of vaginal DHEA requires further research in women with a history of cancer.

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Figure 1.
CONSORT diagram

Figure 2.
 Mean change in severity of dryness or dyspareunia over 12 weeks

Table 1

Baseline Demographic and Treatment Characteristics

Demographic Characteristics	Treatment Arm			P Value
	Plain Moisturizer N=147	3.25 mg DHEA N=147	6.5 mg DHEA N=149	
Age in years (SD)	58 (7.3)	56.8 (6.7)	57.3 (8.2)	0.63
Race (%):				
White	137 (93%)	142 (97%)	142 (95%)	0.63
Black/AA	7 (5%)	3 (2%)	5 (4%)	
Asian	1 (1%)	0	0	
Missing	2 (1%)	2 (1%)	2 (1%)	
Menopause-natural	95 (65%)	98 (67%)	88 (59%)	0.37
Bilateral oophorectomy	48 (33%)	43 (30%)	55 (37%)	0.38
Weight in kg (SD)	75 (16.6)	77 (14.7)	73 (14.8)	0.06
Height in cm (SD)	163.2 (6.6)	164.4 (6.0)	163.1 (6.8)	0.20
TREATMENT CHARACTERISTICS:				
Breast	142 (97%)	143 (97%)		0.70
Ovarian	3 (2%)	4 (3%)	3 (2%)	
Endometrial	2 (1%)	0	2 (1%)	
Tamoxifen current	23 (16%)	22 (15%)	24 (16%)	0.96
AI current:				
Anastrozole/Letrozole	72 (49%)	71 (48%)	72 (48%)	1.0
Exemestane	9 (6%)	11 (8%)	10 (7%)	
Months on current therapy (SD)	22 (18.7)	21.1 (17.1)	24.5 (18)	0.31

Table 2

Change from baseline to 12 weeks in self-reported side effects, negative change indicates worsening symptom, range 0–10

Side Effect	Plain Moisturizer Mean (SD) (95% CI) N=118	3.25 mg DHEA Mean (SD) (95% CI) N=123	6.5 mg DHEA Mean (SD) (95% CI) N=112
Vaginal discharge	−0.7 (2.6) (−1.1, −0.2)	−0.8 (2.3) (−1.3, −0.4)	−0.7 (2.3) (−1.2, −0.3)
Rash in vaginal area	0.1 (1.6) (−0.2, 0.4)	0.1 (1.3) (−0.1, 0.3)	−0.1 (0.8) (−0.3, 0)
Unwanted hair growth	0.7 (2.4) (0.2, 1.1)	0.4 (2.1) (0.1, 0.8)	0.3 (1.7) (0, 0.6)
Unwanted hair loss	0.3 (1.9) (−0.1, 0.6)	0 (1.5) (−0.2, 0.3)	0.2 (1.5) (0, 0.5)
Change in voice	0.2 (1.2) (0, 0.4)	−0.1 (0.7) ** (−0.3, 0)	−0.2 (1.1) ** (−0.4, 0)
Acne	0.1 (1.5) (−0.2, 0.4)	−0.2 (1.8) (−0.5, 0.1)	−0.3 (1.9) (−0.6, 0.1)
Headaches	0.5 (2.2) (0.1, 0.9)	−0.2 (2.0) * (−0.5, 0.2)	−0.1 (2.2) (−0.5, 0.3)
Breast pain	0.3 (1.6) (0, 0.6)	0.3 (1.5) (0, 0.5)	0.4 (1.8) (0, 0.7)

* Significantly different versus Plain Moisturizer,

* p<.05,

** p .02

Table 3

Mean scores and change from baseline for select Female Sexual Function Index (FSFI) subscales and Quality of Life (QOL). Positive change = better function

FSFI Subscale	Plain Moisturizer Mean (SD) (95% CI) N=118	3.25 mg DHEA Mean (SD) (95% CI) N=123	6.5 mg DHEA Mean (SD) (95% CI) N=112
Arousal			
Baseline	2.1 (1.8) (1.8, 2.3)	2.1 (1.7) (1.8, 2.4)	1.9 (1.7) (1.7, 2.2)
12 week	2.5 (1.8) (2.2, 2.9)	2.8 (1.9) (2.5, 3.2)	3.0 (1.7) (2.7, 3.3)
Change	0.4 (1.6) (0.1, 0.7)	0.7 (1.4) * (0.4, 1.0)	1.0 (1.6) ** (0.7, 1.2)
Lubrication			
Baseline	1.4 (1.2) (1.2, 1.6)	1.5 (1.3) (1.3, 1.7)	1.4 (1.3) (1.1, 1.6)
12 week	2.5 (1.9) (2.1, 2.8)	2.8 (2.0) (2.5, 3.2)	3.0 (2.0) (2.6, 3.4)
Change	1.1 (1.7) (0.7, 1.4)	1.3 (1.8) (1.0, 1.6)	1.6 (1.7) * (1.3, 1.9)
Satisfaction			
Baseline	2.9 (1.6) (2.6, 3.1)	2.7 (1.7) (2.4, 2.9)	2.7 (1.6) (2.4, 3.0)
12 week	3.4 (1.8) (3.1, 3.7)	3.6 (1.8) (3.3, 3.9)	3.8 (1.6) (3.5, 4.1)
Change	0.5 (1.5) (0.2, 0.8)	0.9 (1.5) (0.7, 1.2)	1.1 (1.6) * (0.8, 1.4)
Pain			
Baseline	1.6 (1.4) (1.4, 1.9)	1.6 (1.5) (1.4, 1.9)	1.4 (1.3) (1.2, 1.6)
12 week	2.5 (2.0) (2.1, 2.8)	3.0 (2.0) (2.7, 3.4)	3.5 (2.0) (3.1, 3.9)
Change	1.0 (1.8) (0.6, 1.3)	1.4 (1.7) * (1.1, 1.7)	2.0 (1.6) *** (1.7, 2.3)

FSFI Subscale	Plain Moisturizer Mean (SD) (95% CI) N=118	3.25 mg DHEA Mean (SD) (95% CI) N=123	6.5 mg DHEA Mean (SD) (95% CI) N=112
Overall Total			
Baseline	12.2 (7.5) (11.0, 13.5)	12.5 (7.9) (11.2, 13.8)	11.6 (7.3) (10.4, 12.8)
12 week	16.2 (9.3) (14.5, 17.9)	17.9 (9.6) (16.2, 19.7)	19.1 (8.7) (17.5, 20.7)
Change	3.8 (7.4) (2.4, 5.1)	5.5 (7.5) (4.2, 6.8)	7.1 (7.3) *** (5.8, 8.5)
QOL			
Baseline	7.6 (2.0)	7.3 (1.8)	7.5 (1.8)
12 week	7.4 (2.3)	7.5 (1.7)	7.8 (1.7)
Change	-0.3 (2.2)	0.2 (1.7)	0.3 (1.9) **

Significant difference versus Plain Moisturizer :

*
p .05,

**
p .01,

p .001