# Final Report

## A 12 week, Multi-center, Double-blind, Randomized, Placebo-controlled Clinical Trial for the Evaluation of the Efficacy and Safety of PAC-EX01 (EstroG-100®) on Menopausal Symptoms

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| **Test Material** | PAC-EX01 (EstroG-100®) |
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| **Investigators:** | Tak Kim, MD<br>Department of Obstetrics and Gynecology, Korea University Anam Hospital<br><br>Seok-Kyo Seo, MD<br>Department of Obstetrics and Gynecology, Yonsei University College of Medicine Severance Hospital |
| **Study Location:** | - Department of Family Medicine, Ajou University Medical Center, 164, World cup-ro, Yeongtong-gu, Suwon-shi, Gyeonggi-do, 443-380, South Korea<br>- Department of Obstetrics and Gynecology, Korea University Anam Hospital, 73, Inchon-ro, Seongbuk-gu, Seoul 136-705, South Korea<br>- Department of Obstetrics and Gynecology, Yonsei University College of Medicine Severance Hospital, 50 Yonsei-ro, Seodaemun-gu, Seoul, 120-752, South Korea |
| **Name of sponsor:** | Naturalendo Tech Co., Ltd<br>3rd Fl., Cs Tower, 58, 255 st., Pankyo-ro, Bundang-gu, Seongnam-shi, Gyonggi-do 463-400, South Korea |

This research was carried out according to International Conference on Harmonization / WHO Good Clinical Practice Standards (ICH-GCP)

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## Brief of Protocol

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| 1. Title | A 12 week, multi-center, double-blind, randomized, placebo-controlled clinical trial for the evaluation of the efficacy and safety of PAC-EX01 (EstroG-100®) on menopausal symptoms |
| 2. Protocol Number: | NE_PAC-EX01<br>Version No.: 4.1 |
| 3. Objective | To evaluate efficacy and safety to observe changes in quality of life and the symptoms of menopause after the administration of PAC-EX01 (EstroG-100) compared to placebo with pre-, peri-, postmenopausal ladies. |
| 4. Test Period | 12 weeks |
| 5. Dosage | Take one tablet including 257mg of PAC-EX01 orally twice a day or placebo |
| 6. Test Method | Multi-center, randomized, double-blind and placebo-controlled study. |
| 7. Eligibility / Exclusion Criteria | Eligibility |
| | Any women with moderate to severe menopausal symptoms identified by simplified questionnaire of Kupperman Menopause Index (KMI) with score of greater than or equal to 20 (≥ 20) at the age of 40 to 70 |
| | Exclusion Criteria |
| | - Body Mass Index ≥ 30 kg/$m^2$<br>- History of using estrogen or progestin-containing products and of taking phytoestrogen in past 3 months<br>- Subject with history or potential of being diagnosed with hormone-dependent cancer (endometrial hyperplasia, uterine cancer, breast cancer, mastopathy)<br>- Subject with history of severe migraines, thromboembolism, cerebrovascular disease, myocardial infarction, unstable angina pectoris<br>- Subject with history of mental disorder (depression, anxiety disorder, etc.) and/or use of medication for mental disorder<br>- Irregular gynecological bleeding after 1 year of menopause<br>- Uncontrolled hypertension, thyroids disease, and diabetes mellitus<br>- Drug and alcohol abuse<br>- ALT or AST 3 times higher than the max. normal value<br>- Creatine 2 times higher than the max. normal value<br>- Abnormality in mammogram≥ 3 (BI-RADS Category) or PAP smear (ASCUS acceptable)<br>- Subject with history of participating in another clinical study within the past 1 month or planning to participate in other clinical studies while enrolled in this study<br>- The evaluator determines the subject is inappropriate to be enrolled in this study<br>- Women with thyroid hormone medicine, clonidine, anticoagulant or antithrombotic product use within the last 3 months<br>- Women with menopause related medicine and/or supplement intake within the last 1 month<br>- Women with intake of food containing *Cynanchum wilfordii*, *Phlomis umbrosa*, *Angelica gigas* within the last 1 month |
| 8. Study participant | 104 female participants of age of 40~70 with menopausal symptoms |

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| 9. Statistical Analysis | The evaluation variable of efficacy before and after administration was analyzed by using paired t-test, and the difference between groups was compared by using two sample t-test and Wilcoxon rank sum test for evaluating statistical differences. |

## Study Flow Chart of Evaluation

| | Visit 1 | Visit 2 (Week 0) | Visit 3 (Week 4) | Visit 4 (Week 12) | Remarks |
|---|---|---|---|---|---|
| Questionnaire | ◎ | | ◎ | ◎ | |
| Prequalification Testing | ◎ | | | | |
| Anthropometric measurement | ◎ | | | ◎ | |
| Biochemical measurement | ◎ | | | ◎ | |
| Interview with Physician | ◎ | | ◎ | ◎ | |
| Enrollment and Randomization | | ◎ | | | |
| Allocation of test materials | | ◎ | | | |

**Primary Endpoints**

Mean change in quality of life using index of questionnaire (Kupperman Menopause Index or KMI) of moderate to severe menopausal symptoms from baseline to week 12

**Secondary Endpoints**

Mean change in scores of the 12 individual menopausal symptom of KMI from baseline to week 12

**Measurements**

1) Biochemical and hematological analysis
- Serum metabolic markers: alkaline phosphatase, triglyceride, low density lipoprotein, high density lipoprotein, and total cholesterol
- Serum safety factors: white blood cell, red blood cell, hemoglobin, Hematocrit, platelet, alanine aminotransferase, aspartate aminotransferase, creatinine, total protein, albumin, fasting glucose
- Serum hormonal: estradiol (E2), follicle stimulating hormone (FSH), Endometrial Thickness

2) Anthropometric measurements: body weight and BMI

3) Screening tests plus interview and evaluation by physician
- Cardiovascular disease-related medical events will be checked by physician.
- Mammograms and PAP smear will be completed for exclusion prior to clinical trial.

**※ PAC-EX01 was assigned as a code for EstroG-100 in this clinical trial.**

## 1. Title

A 12 week, multi-center, double-blind, randomized, placebo-controlled clinical trial for the evaluation of the efficacy and safety of PAC-EX01 (EstroG-100®) on menopausal symptoms

## 2. Principal Investigator & Investigators


2.1. Principle Investigator

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## 3. Sponsor


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## 4. Background Information

EstroG-100 is a standardized herbal root extract of *Cynanchum wilfordii, Phlomis umbrosa,* and *Angelica gigas.* It is hot water extracted and filtered to remove insoluble fiber and dried to fine powder. The Ministry of Food and Drug Safety (MFDS) in Korea has since registered these herbs as non-toxic food materials based on the fact that they have been used as safe foods for herbal remedies for several hundred years in Korea and China.

There have been number of studies, both in-vitro as well as in-vivo studies, that have confirmed the safety and efficacy of EstroG-100.

In e-screen assay to measure the alkaline phosphatase (ALP) level in non-reproductive tract target tissue response, *Cynanchum wilfordii*, *Phlomis umbrosa*, and *Angelica gigas* in combination were found to promote ALP activity level more than any of the individual herbal extract alone. There appears to be synergistic effect of the three herbal extracts.

Safety of EstroG-100 has been well studied and established. In addition to the receptor binding affinity test performed by Chungbuk National University in South Korea which did not show any affinity of EstroG-100 to both Estrogen receptor alpha and beta, in the ovariectomized (OVX) rat experiment by College of Veterinary Medicine and Research Institute of Veterinary Medicine, Chungbuk National University, results showed that oral administration of EstroG-100 for 12 weeks did not increase uterus weight. Significant

increase in the femoral bone mineral density was observed in the rats given EstroG-100 compared to the control group. No serious side effect was seen in ovariectomized rat experiment. Safety of the product was also supported by single-dose, 3 month long multi-dose toxicity and genetic toxicity test which showed no toxic event.

In one of the previous two human studies conducted at Samsung Cheil Hospital, School of Medicine, Sungkyungwan University in South Korea, the treatment group on EstroG-100 and vitamins and minerals showed statistically significant improvement in various menopausal symptoms including hot flush, sleep disorder, mental awareness, joint pain, dyspepsia, urinary incontinence, and fatigue compared to that of placebo. The treatment group showed more than 5 times better improvement in symptoms compared to that of placebo group.

In the other human study conducted in California, United States, EstroG-100 showed statistically significant improvement in quality of life as well as in 10 different menopausal symptoms including vasomotor, paresthesia, insomnia, nervousness, vertigo, fatigue, rheumatic pain, formication and vaginal dryness compared to placebo group.

According to reports on Korean herbs to WHO, *Cynanchum wilfordii* and *Phlomis umbrosa* have hepatoprotective and antihepatotoxic activity, respectively.

## 5. Purpose

The purpose of this study is to observe with the more participants in multi-centers how the oral administration of EstroG-100 changes the menopausal symptoms on pre-, peri-, and post-menopausal women including vasomotor, paresthesia, trouble sleeping, nervousness, melancholia, vertigo, fatigue, rheumatic pain, headache, palpitation, formication, and vaginal dryness.

## 6. Study Method

This clinical study was approved on January 17th, 2014, December 12th, 2013 and December 16th, 2013 by each IRB of Ajou University Medical Center, Korea University Anam Hospital and Yonsei University College of Medicine Severance Hospital, respectively.

Participants who were on supplements specifically for menopause were instructed at the first visit to stop prior to starting test material for the research. At every visit, all the participants were advised not to take any hormone replacement therapy or menopausal symptoms related supplements during the clinical study.

This research was carried out according to International Conference on Harmonization / WHO Good Clinical Practice standards (ICH-GCP)

### 6.1. Study group

After the screening for the study, 105 female participants with menopausal symptoms were randomized to receive either EsttroG-100 or placebo. Criteria for eligibility was any woman of the age of 40 to 70 with moderate or severe menopausal symptoms identified by a simplified questionnaire with Kupperman Menopause Index (KMI) > or =20. Exclusion criteria include subjects with any of the following conditions:

- Body mass index $\geq 30$ kg/m$^2$

- History of using estrogen or progestin-containing products in past 3 months
- Subject with history or potential of being diagnosed with hormone-dependent cancer (endometrial hyperplasia, uterine cancer, breast cancer, mastopathy)
- Subject with history of severe migraines, thromboembolism, cerebrovascular disease, myocardial infarction, unstable angina pectoris
- Subject with history of mental disorder (depression, anxiety disorder, etc.) and/or use of medication for mental disorder
- Irregular gynecological bleeding after 1 year of menopause
- Uncontrolled hypertension, thyroids disease, and diabetes mellitus
- Drug and alcohol abuse
- Abnormality in renal and/or liver function
- Abnormality by mammography≥ 3 (BI-RADS Category) or PAP smear (ASCUS acceptable)
- Subject with history of participating in another clinical study within the past 1 month or planning to participate in other clinical studies while enrolled in this study
- The evaluator determines the subject is inappropriate to be enrolled in this study
- Any woman with thyroid hormone medicine, clonidine, anticoagulant or antithrombotic product use within the last 3 months
- Any woman with menopause related medicine and/or supplements intake within the last 1 month
- Any woman with intake of food containing *Cynanchum wilfordii*, *Phlomis umbrosa*, *Angelica gigas* within the last 1 month

Informed consents were confirmed. After written consent of the participants, their eligibilities were reexamined with the results of laboratory, mammogram, and PAP smear. Randomized numbers were allocated to qualified participants. Participants with individual serial numbers are regarded as registered participants. The registered participants were reminded that they should not take estrogen- or progestin-containing products nor menopausal symptom related supplements during the course of this study. In addition, the enrolled participants were informed to maintain the normal life style (exercise, smoking) and dietary pattern, and to maintain them as similar to before the study, without exposing themselves to overeating, bulimia, binge-eating, binge-drinking, and excessive stress.

6.2. Dosage

PAC-EX01 or EstroG-100 is a mixed root extract of *Cynanchum wilfordii* 32.5%, *Phlomis umbrosa* 32.5%, *Angelica gigas* 35%. EstroG-100 tablet included 257.00 mg of EstroG-100, corn starch 145.31 mg, microcrystalline cellulose 191.40 mg, silicon dioxide 6.38 mg, magnesium stearate 9.57mg, hydroxypropyl methyl cellulose 19.14 mg, titanium dioxide 4.4 mg, glycerin mono fatty acid ester 1.91 mg, and cochineal extract 2.87 mg. Placebo tablet consisted of corn starch 402.32 mg, microcrystalline cellulose 191.4 mg, Silicon dioxide 6.38mg, Magnesium stearate 9.57mg, hydroxypropyl methyl cellulose 19.14 mg, titanium dioxide 4.4 mg, glycerin mono fatty acid ester 1.91 mg, and cochineal extract 2.87 mg. Placebo tablet maintains the same formula except for corn starch replacing EstroG-100. Study and placebo materials were separately formulated into 638mg

tablets in purple color and packed in the bottles with the same color and appearance so that both doctors and patients may not know the difference from the external appearances. Participants were administered the study material as one tablet twice a day orally for 12 weeks. Each participant was given a bottle at week 0 (visit 2) and 4 (visit 3).

6.3 Study period: March 6th ~ August 21st, 2014 (from 1st participant to last visit of last participant)

6.4 Observation and test items

All participants visited the respective hospital 4 times with each visit summary as follows:

6.4.1. Visit 1 (Screening and recruiting of participants)

1) Informed Consent form confirmed
2) Anthropometric measurement including height, weight, BMI, drinking and smoking
3) Screening tests plus interview and evaluation by physician for exclusion criteria
   - Cardiovascular disease-related medical events checked by physician
   - Interview
4) Vital signs (pulse, and blood pressure)
5) Participant self-scoring of each question in the Kupperman Menopause Index (KMI) and the score of vaginal dryness (sensation of dryness or burning in the vagina; difficulty with sexual intercourse); KMI includes hot flush or cold sweat (vasomotor), numbness and tingling (paresthesia), trouble sleeping (insomnia), nervousness, feeling blue or depressed (melancholia), dizzy spells (vertigo), tired feelings (fatigue), rheumatic pain (arthralgia and myalgia), headaches, pounding of the heart (palpitation), and sensation of crawling on the skin (formication).
6) Randomization has been done according to the random number generated by SAS system into 2 strata, with Stratum 1: KMI 30 or less and Stratum 2: KMI more than 30. If $20 \leq$ the index $\leq 30$, the participants belong to the serial number of 001 to 050. If the index $\geq 30$, the participant is numbered to one of the serial number of 051 to 100. Each investigator assigned the following screening number to participant: AA-S ZZZ wherein AA is investigation hospital (Ajou Univ 01, Korea Univ 02, and Yonsei Univ 03) and ZZZ is serial number while S stands for screening. Double blind trial was performed. The patients was randomly allocated to either study group or control group. Study and placebo materials will be manufactured in same color tablets and packed in the same bottles so that both doctors and patients will not know the difference from the external appearance.
7) Biochemical and hematological analysis
   - Serum metabolic markers: alkaline phosphatase (ALP), triglyceride (TG), low density lipoprotein (LDL), high density lipoprotein (HDL) and total cholesterol (Chol)
   - Serum safety markers: white blood cell (WBC), red blood cell (RBC), hemoglobin, hematocrit, platelet, alanine aminotransferase (AST), aspartate aminotransferase (ALT),

creatinine, total protein, albumin, fasting glucose

- Serum hormones: estradiol (E2), follicle stimulating hormone (FSH), Endometrial Thickness

8) Mammogram/PAP smear test
9) Eligibility
10) Contacted and instructed the qualified participants to visit to see the doctor as soon as possible for enrollment.

6.4.2. Visit 2 (Week 0)

This visit will be made within 14 days after first visit, the evaluation items are indicated below:

1) Examine the history of previous medication
2) Physical examination
3) Blood test for safety evaluation
4) Measurement of endometrial thickness
5) Enrolled and randomized

- The qualified participants were randomly allocated with new serial number in the form of AA-R ZZZ wherein AA is study location number as shown in 6) of 6.4.1 above and ZZZ serial number while R stands for randomization.
- 51 assigned to treatment group (EstroG-100 group) and 54 to placebo group.
- Allocation of pill bottle

6.4.3. Visit 3 (Week 4)

This visit will be made within ±7 days after 4 weeks from the week 0, the evaluation items are indicated below:

1) Check the adverse effect
2) Check the Concomitant medication
3) Physical examination
4) Measurement of vital signs (blood pressure, pulse) and anthropometry investigation(weight)
5) Check the intake compliance
6) Participant self-scoring of each question in the Kupperman Menopause Index
7) New bottle was given to participant

6.4.4. Visit 4 (Week 12)

This visit will be made within ±5 days after 84 days from week 0, the evaluation items are indicated below:

1) Check the adverse effect
2) Check the concomitant medication
3) Physical examination
4) Measurement of vital signs (blood pressure, pulse) and anthropometry investigation(weight)
5) Check the intake compliance

6) Biochemical and hematological analysis
   - Serum metabolic markers: alkaline phosphatase (ALP), triglyceride (TG), low density lipoprotein (LDL), high density lipoprotein (HDL), and total cholesterol (Chol)
   - Serum safety markers: white blood cell (WBC), red blood cell (RBC), hemoglobin, hematocrit, platelet, alanine aminotransferase (AST), aspartate aminotransferase (ALT), creatinine, total protein, albumin, fasting glucose
   - Serum hormones: estradiol (E2), follicle stimulating hormone (FSH)
7) Participant self-scoring of each questions in the Kupperman Menopause Index
8) Measurement of endometrial thickness

6.5 Evaluation

6.5.1. Efficacy:

6.5.1.1 Primary endpoint: Quality of life using KMI (Kupperman index) total score

6.5.2.2 Secondary endpoint: The individual symptom of the KMI and vaginal dryness

6.5.2. Safety

- Laboratory testing for serum safety markers and interview
- Weight, BMI, serum hormone level

6.6 Premature termination

For the detection of cases of adverse events, every subject was interviewed by the physician at each visit. In the cases of adverse events, the physician made the decision on continuation of study of the subject and provided appropriate recommendations. In addition, participants were contacted via telephone for any adverse event monitoring every two weeks and compliance with the study. If any participant did not come by test protocol or were later found to belong to exclusion criteria, she shall be in principle dropped out.

## 7. Data Analysis

SAS® (Version 9.2, SAS Institute, Cary, North Carolina, USA) was used for the statistical analysis.

7.1. Statistical analysis of efficacy

The evaluation variable of efficacy before and after administration was analyzed by using paired t-test, and the difference between groups was compared by using two sample t-test and Wilcoxon rank sum test for evaluating statistical differences

7.2. Statistical analysis of safety

7.2.1. Adverse Events

All adverse event rates reported during the trial period was assessed by charting all adverse event

incidences of the test subjects. The ratio of test subjects with adverse events in each group was analyzed by using chi-square test or fisher's exact test.

7.2.2. Clinical Pathology

Continuous type of results within group, such as hematological and blood chemistry tests, used paired t-test, and between groups, two sample t-test was used. In case of some measurement variables in the urine test, the results were divided into normal and abnormal and within group differences were analyzed by McNemar's test

7.2.3. Vital Signs

Weight, blood pressure, and pulse were checked during each visit, and the difference before and after the administration within group used paired t-test, and between groups used two sample t-test.

## 8. Study Result

8.1 Enrollment

The effectiveness of EtroG-100 were evaluated in 96 participants out of total 105 participants enrolled in the study and complied with the dosage protocol of 12 weeks (Visit 4).

- 1 participant who could not be reached for the 4$^{th}$ week visit was terminated from the study for her withdrawal of the consent form
- 2 participants were terminated from the study at the time of screening for enrollment for errors in mammography
- 1 participant who could not be reached for the 4$^{th}$ week visit was terminated for her taking of flu medication
- 1 participant was terminated at the time of screening for enrollment for her too high triglyceride level and abnormal hypertension
- 1 participant was terminated at the time of screening for enrollment for her BMI is equal to or higher than 30
- 1 participant was terminated at the time of screening for enrollment for her blood concentration of E2 is in the range of 200 ~ 400 pg/ml that is the typical level of women in the late follicular phase well before menopause
- 1 participant dropped before week 4 for her withdrawal of the consent form due to the occurrence of palpitation
- 1 participant dropped before week 12 for her taking of hormone-related medication was included in the evaluation

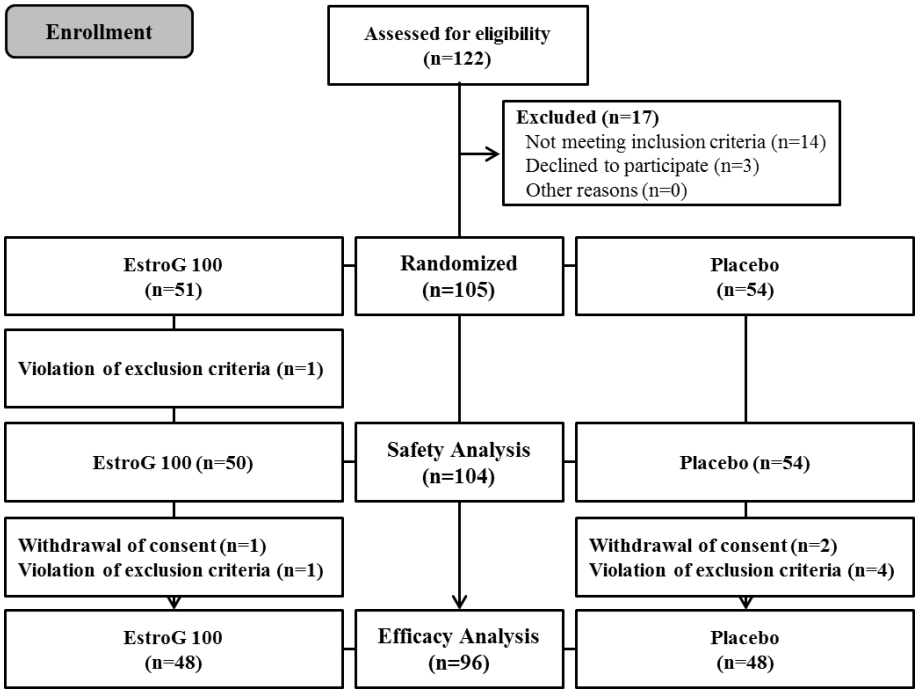


Fig. 1. Study Flow diagram

8.2 General characteristics of the study group at baseline

Total number of evaluated participants for safety analysis was 104. 54 participants were in the placebo group and 50 participants in EstroG-100 group. Average age of the 50 participants in EstroG-100 group was 53.48±6.46 (range from 40 to 66) while that in placebo group was 54.56±5.62 (range from 40 to 67). Age distribution of the participants is noted in Table 1, and there is no significant difference between the EstroG-100 group and the placebo group (Table 1).

Table 1. Demographic characteristics (Safety set)

| Group | | EstroG-100 | Placebo |
|---|---|---|---|
| No. of Participants | | 50 | 54 |
| Age | Average | 53.50±6.47 | 54.57±5.66 |
| | Min. – Max. | 40 – 66 | 40 – 67 |

p>0.05, t-test

At the baseline of the study, there were no significant differences on basic physical profiles, serum hormone concentrations, and serum metabolic profiles between the treatment group and the placebo group (Table 2).

Table 2. Basic characteristics of subjects (Safety Set)

| | EstroG-100 | Placebo |
|---|---|---|
| Alkaline phosphatase (IU/L) | 60.32±16.82 | 64.76±20.07 |
| Triglyceride (mg/dL) | 95.98±37.13 | 107.93±65.66 |

| | | |
|---|---|---|
| LDL (mg/dL) | 129.72±34.43 | 125.69±33.75 |
| HDL (mg/dL) | 61.88±12.00 | 59.09±14.23 |
| Total cholesterol (mg/dL) | 212.44±36.83 | 203.67±34.91 |
| White blood cell ($10^3/\mu L$) | 5.86±1.23 | 6.07±1.34 |
| Red blood cell ($10^6/\mu L$) | 4.43±0.29 | 4.34±0.27 |
| Hemoglobin (g/dL) | 13.54±0.83 | 13.24±0.97 |
| Hematocrit (%) | 40.19±2.51 | 39.23±2.59 |
| Platelet ($10^3/\mu L$) | 239.84±40.75 | 241.06±40.51 |
| Alanine aminotransferase (IU/L) | 18.54±8.99 | 20.65±11.93 |
| Aspartate aminotransferase (IU/L) | 22.70±5.32 | 24.44±8.35 |
| Creatinine (mg/dL) | 0.73±0.14 | 0.74±0.13 |
| Protein (g/dL) | 7.19±0.41 | 7.20±0.36 |
| Albumin (g/dL) | 4.47±0.24 | 4.46±0.20 |
| Fasting glucose (mg/dL) | 94.72±8.92 | 96.67±7.45 |
| E2 (Pg/ml) | 21.93±24.24 | 31.10±51.23 |
| FSH (mIU/ml) | 60.74±32.30 | 57.78±32.56 |
| Weight (kg) | 56.98±7.04 | 59.06±7.88 |
| Systolic pressure (mmHg) | 120.00±13.52 | 119.87±12.18 |
| Diastolic pressure (mmHg) | 74.10±10.48 | 72.00±10.12 |

No significant difference observed between placebo and treatment groups ($p>0.05$)
HDL, high density lipoprotein; LDL, low density; E2, estradiol; FSH, follicular stimulating hormone; BMI, body mass index

8.3. Efficacy

Among 105 of enrolled participants, 9 participants were dropped from the study for the exclusion criteria. 48 participants were in the placebo group and 48 participants in EstroG-100 group.

The mean KMI score was significantly reduced in EstroG-100 group from 35.42±7.96 at baseline to 23.40±9.25 at week 4 and to 14.85±10.04 at week 12 while placebo group showed changes from 33.25±7.78 at baseline to 24.56±9.34 at week 4 and to 19.85±10.37 at week 12 ($p<0.01$). The decrease in KMI score at week 12 was 20.56±12.06 in the treatment group while it was 13.40±13.30 in the placebo group. The improvement of quality of life was statistically significant in comparison with the two groups ($p<0.01$). Comparative changes in climacteric symptoms between the EstroG-100 group and the placebo group are illustrated on Table 3 and Fig. 2.

Table 3. Mean change in Kupperman Menopause Index

| | EstroG-100<br>N=48<br>Mean±SD | Placebo<br>N=48<br>Mean±SD |
|---|---|---|
| Week0 (Baseline) | 35.42±7.96 | 33.25±7.78 |
| Week4 | 23.40±9.25 | 24.56±9.34 |
| Change from baseline | -12.02±10.50$^{*\,\#\#}$ | -8.69±8.80$^{\#\#}$ |
| Week12 | 14.85±10.04 | 19.85±10.37 |
| Change from baseline | -20.56±12.06$^{**\,\dagger\dagger\,\#\#}$ | -13.40±13.30$^{\#\#}$ |

*, p<0.05 compared between groups by t-test
**, p<0.01 compared between groups by t-test
††, p<0.01 compared between groups by Wilcoxon rank sum test
##, p<0.01 compared to baseline to baseline by paired t-test

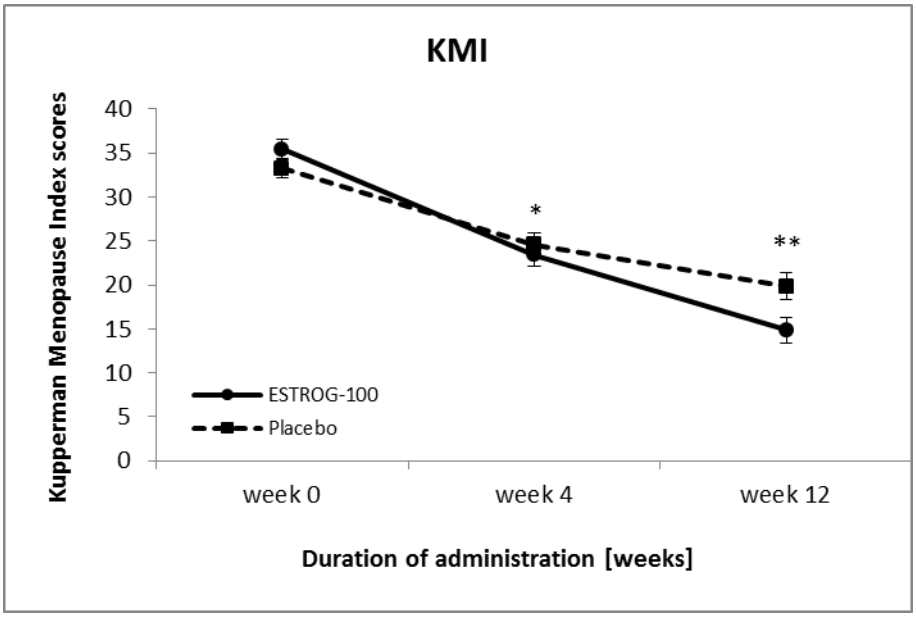


**Fig. 2. Changes of Kupperman Menopause Index (Mean±SE) during 12 weeks administration of EstroG-100 and placebo.**
SE: Standard Error, *: Statistically significant compared between groups; p<0.05
**: Statistically significant compared between groups; p<0.01 by t–test

As for the individual symptom of KMI, the mean score of vasomotor (=hot flush or cold sweat) was significantly lowered in EstroG-100 group. The test group showed changes from 2.15±0.87 at baseline to 1.56±0.94 at week 4 and to 0.85±0.92 at week 12 (p<0.01) while that of placebo group was also significantly decreased from 2.10±0.86 at baseline to 1.69±0.88 at week 4 and to 1.23±0.86 at week 12 (p<0.01). The decrease in the hot flush score at week 12 (1.29±1.09 in EstroG-100 vs. 0.88±1.16 in placebo) was significant (p<0.05) between both groups. The result of improvement in hot flush is shown in Table 4 and Fig. 3.

Table 4. Mean change in scores of the individual symptom of KMI (Hot Flush, Paresthesia, Insomnia and Nervousness)

| | | EstroG-100 N=48 Mean±SD | Placebo N=48 Mean±SD |
|---|---|---|---|
| Hot flush or cold sweat (=vasomotor) | Week 0 (Baseline) | 2.15±0.87 | 2.10±0.86 |
| | Week 4 | 1.56±0.94 | 1.69±0.88 |
| | Change from baseline | -0.58±1.01## | -0.42±0.85## |
| | Week 12 | 0.85±0.92 | 1.23±0.86 |
| | Change from baseline | -1.29±1.09*†## | -0.88±1.16## |
| Numbness and tingling (=paresthesia) | Week 0 (Baseline) | 2.08±0.82 | 1.88±0.87 |
| | Week 4 | 1.27±0.84 | 1.46±0.90 |
| | Change from baseline | -0.81±0.87*†## | -0.42±0.90## |
| | Week 12 | 0.92±0.85 | 1.23±0.93 |
| | Change from baseline | -1.17±1.04*†## | -0.65±1.19## |
| Trouble sleeping (=insomnia) | Week 0 (Baseline) | 2.44±0.80 | 2.25±0.76 |
| | Week 4 | 1.54±0.99 | 1.44±1.11 |
| | Change from baseline | -0.90±1.08## | -0.81±1.10## |
| | Week 12 | 1.08±0.99 | 1.23±1.08 |
| | Change from baseline | -1.35±1.14## | -1.02±1.21## |
| Nervousness | Week 0 (Baseline) | 2.31±0.69 | 2.15±0.80 |
| | Week 4 | 1.52±0.85 | 1.54±0.94 |
| | Change from baseline | -0.79±0.87## | -0.60±0.84## |
| | Week 12 | 0.90±0.78 | 1.19±0.84 |
| | Change from baseline | -1.42±0.99*††## | -0.96±0.99## |

*, $p<0.05$ compared between groups by t-test

†, $p<0.05$ compared between groups; ††, $p<0.01$ compared between groups by Wilcoxon rank sum test

##, $p<0.01$ compared to baseline to baseline by paired t-test

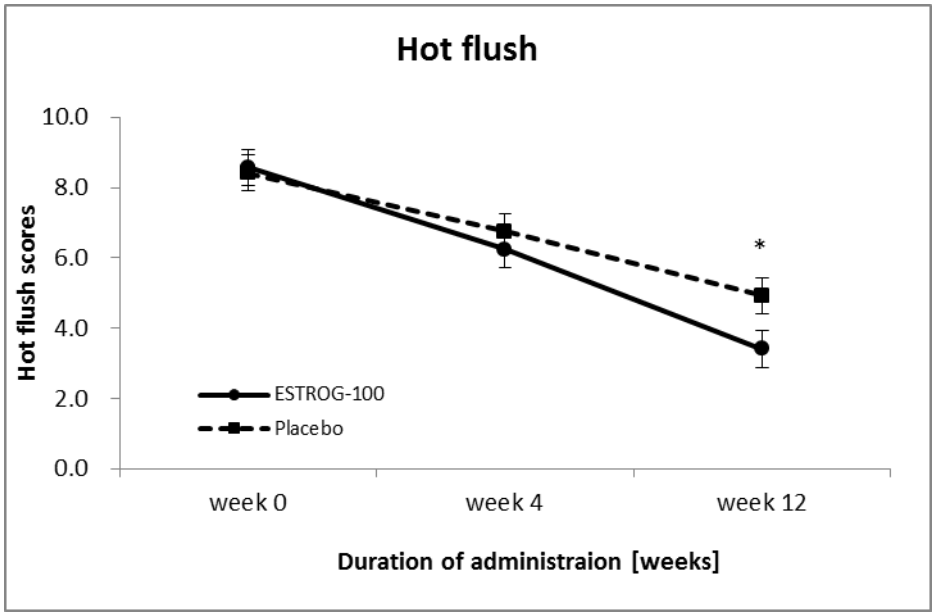


**Fig. 3. Changes of Hot Flush (Mean±SE) during 12 weeks administration of EstroG-100 and placebo.**

SE: Standard Error, *: Statistically significant compared between groups; p<0.05

Significant improvement was found in the mean paresthesia (=numbness and tingling) score. In EstroG-100 group showed improvement from 2.08±0.82 at baseline to 1.27±0.84 at week 4 and to 0.92±0.85 at week 12 (p<0.01). The difference in paresthesia score between the baseline and week 12 was 1.17±1.04 in the test group and 0.65±1.19 in the placebo group. The improvement between the two groups was statistically significant (p<0.05) (Table 4 and Fig. 4).

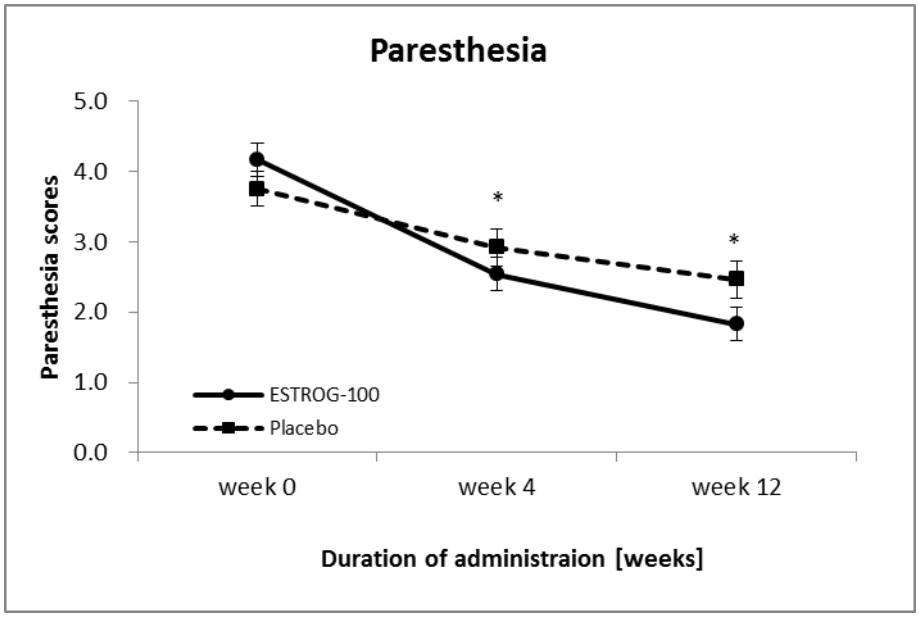


**Fig. 4. Changes of paresthesia (Mean±SE) during 12 weeks administration of EstroG-100 and placebo.**

SE: Standard Error, *: Statistically significant compared between groups; p<0.05 by t–test

The mean insomnia (=trouble sleeping) score was significantly reduced in EstroG-100 group from 2.44±0.80 at baseline to 1.54±0.99 at week 4 and to 1.08±0.99 at week 12 ($p<0.01$). The improvement at week 12 (1.35±1.14 in the EstroG-100 group vs. 1.02±1.21 in the placebo group) was marginally significant between the two groups ($p=0.084$). The improvement of insomnia is shown on Table 4.

The mean nervousness score was significantly reduced in EstroG-100 group from 2.31±0.69 at baseline to 1.52±0.85 at week 4 and to 0.90±0.78 at week 12 ($p<0.01$). The improvement at week 12 (1.42±0.99 in the EstroG-100 group vs. 0.96±0.99 in the placebo group) was significant between the two groups ($p<0.05$). The improvement of nervousness is shown on Table 4 and Fig. 5.

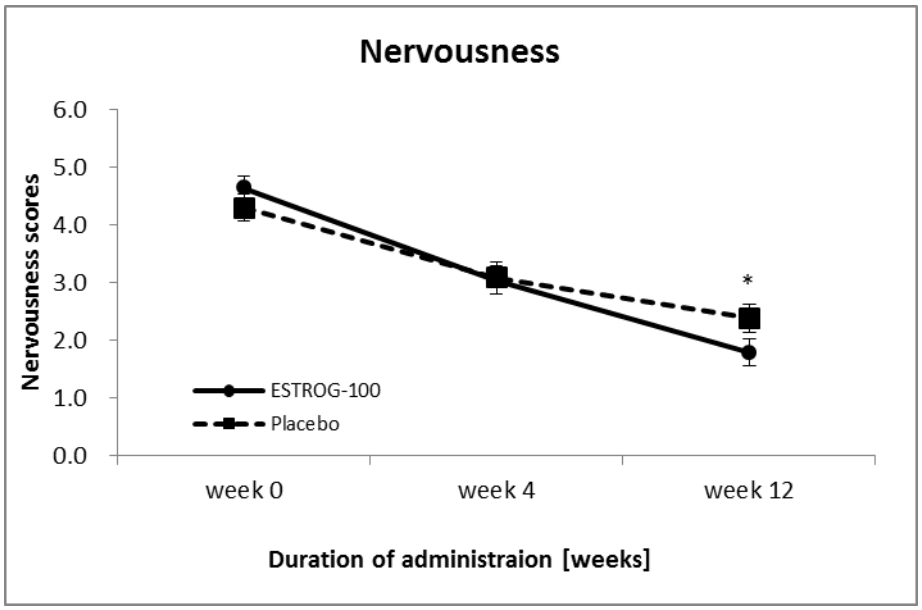


**Fig. 5. Changes of nervousness (Mean±SE) during 12 weeks administration of EstroG-100 and placebo.**

SE: Standard Error, *: Statistically significant compared between groups; $p<0.05$ by t–test

Table 5. Mean change in scores of the individual symptom of KMI (Melancholia, Vertigo, Fatigue and Rheumatic pain)

| | | EstroG-100 N=48 Mean±SD | Placebo N=48 Mean±SD |
|---|---|---|---|
| Feeling blue or depressed (=melancholia) | Week 0 (Baseline) | 2.10±0.81 | 1.90±0.81 |
| | Week 4 | 1.42±0.71 | 1.29±0.87 |
| | Change from baseline | -0.69±0.95$^{\#\#}$ | -0.60±0.82$^{\#\#}$ |
| | Week 12 | 0.90±0.78 | 1.13±0.70 |
| | Change from baseline | -1.21±1.03$^{*\dagger\#\#}$ | -0.77±1.02$^{\#\#}$ |
| Dizzy spells (=vertigo) | Week 0 (Baseline) | 1.65±0.89 | 1.56±0.94 |
| | Week 4 | 1.17±0.88 | 1.06±0.76 |
| | Change from baseline | -0.48±0.95$^{\#\#}$ | -0.50±1.07$^{\#\#}$ |

| | | | |
|---|---|---|---|
| | Week 12 | 0.69±0.80 | 1.06±0.86 |
| | Change from baseline | -0.96±0.90$^{*\,\dagger\,\#\#}$ | -0.50±1.24$^{\#\#}$ |
| Tired feelings (=fatigue) | Week 0 (Baseline) | 2.48±0.65 | 2.13±0.82 |
| | Week 4 | 1.77±0.93 | 1.73±0.89 |
| | Change from baseline | -0.71±0.87$^{*\,\#\#}$ | -0.40±0.76$^{\#\#}$ |
| | Week 12 | 1.25±0.93 | 1.48±0.87 |
| | Change from baseline | -1.23±1.02$^{**\,\dagger\dagger\,\#\#}$ | -0.65±1.08$^{\#\#}$ |
| Rheumatic pain (=arthralgia and myalgia) | Week 0 (Baseline) | 2.19±0.70 | 2.19±0.87 |
| | Week 4 | 1.38±0.91 | 1.75±0.96 |
| | Change from baseline | -0.81±0.94$^{*\,\dagger\,\#\#}$ | -0.44±0.82$^{\#\#}$ |
| | Week 12 | 0.92±0.92 | 1.42±0.87 |
| | Change from baseline | -1.27±0.94$^{**\,\dagger\dagger\,\#\#}$ | -0.77±1.06$^{\#\#}$ |

*, p<0.05 compared between groups **, p<0.01 compared between groups by t-test
†, p<0.05 compared between groups ††, p<0.01 compared between groups by Wilcoxon rank sum test
##, p<0.01 compared to baseline to baseline by paired t-test

The mean melancholia (=feeling blue or depressed) score was significantly reduced in EstroG-100 group from 2.10±0.81 at baseline to 1.42±0.71 at week 4 and to 0.90±0.78 at week 12 (p<0.01). The improvement at week 12 (1.21±1.03 in the EstroG-100 group vs. 0.77±1.02 in the placebo group) was significant between the two groups (p<0.05). The improvement of melancholia is shown on Table 5 and Fig. 6.

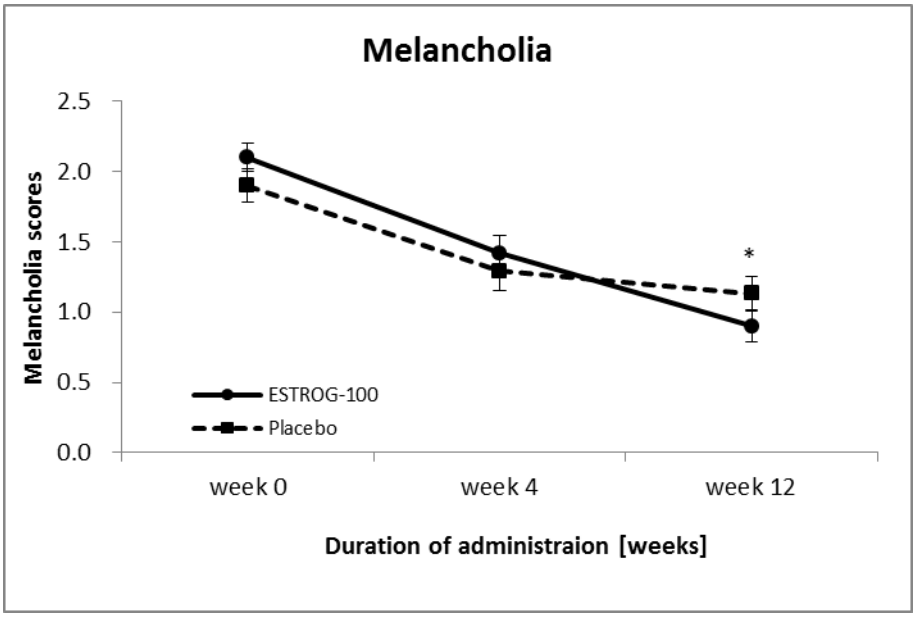


**Fig. 6. Changes of Melancholia (Mean±SE) during 12 weeks administration of EstroG-100 and placebo.**
SE: Standard Error, *: Statistically significant compared between groups; p<0.05 by t–test

The mean vertigo (=dizzy spells) score was significantly reduced in EstroG-100 group from 1.65±0.89 at baseline to 1.17±0.88 at week 4 and to 0.69±0.80 at week 12 (p<0.01). The improvement at week 12 (0.96±0.90 in the EstroG-100 group vs. 0.50±1.24 in the placebo group) was significant between the

two groups (p<0.05). The improvement of vertigo is shown on Table 5 and Fig. 7.

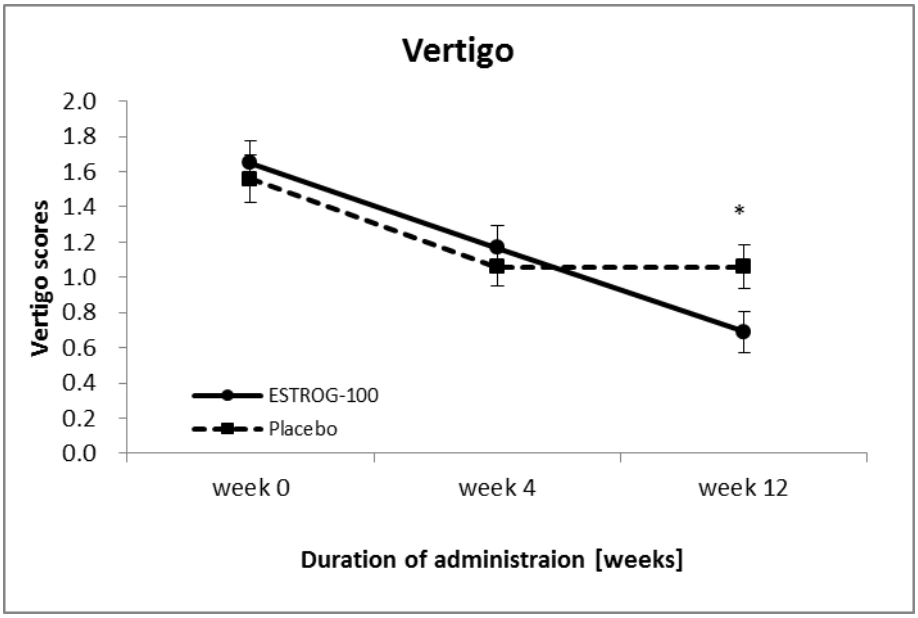


**Fig. 7. Changes of vertigo (Mean±SE) during 12 weeks administration of EstroG-100 and placebo.**

SE: Standard Error, *: Statistically significant compared between groups; p<0.05 by t–test

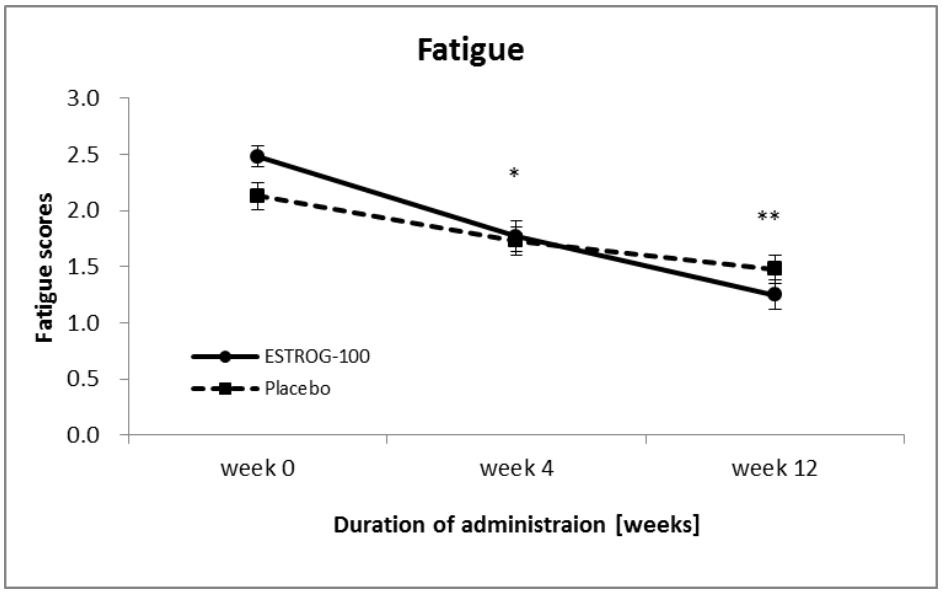


**Fig. 8. Changes of fatigue (Mean±SE) during 12 weeks administration of EstroG-100 and placebo.**

SE: Standard Error, *: Statistically significant compared between groups; p<0.05 by t–test

**: Statistically significant compared between groups; p<0.01 by t–test

Significant improvement was found in the mean fatigue score. In EstroG-100 group showed improvement from 2.48±0.65 at baseline to 1.77±0.93 at week 4 and to 1.25±0.93 at week 12 (p<0.01). The difference in paresthesia score between the baseline and week 12 was 1.23±1.02 in the test group and 0.65±1.08 in the placebo group. The improvement between the two groups was statistically

significant ($p<0.01$) (Table 5 and Fig. 8).

The improvement in rheumatic pain (=arthralgia and myalgia) was also significant between the two groups ($p<0.01$). The mean score was reduced from 2.19±0.70 at baseline to 0.92±0.92 at week 12 in EstroG-100 group. The decrease in the mean score at completion of the study was 1.27±0.94 for EstroG-100 group and 0.77±1.06 for placebo group. This was significant. (Table 5 and Fig.9).

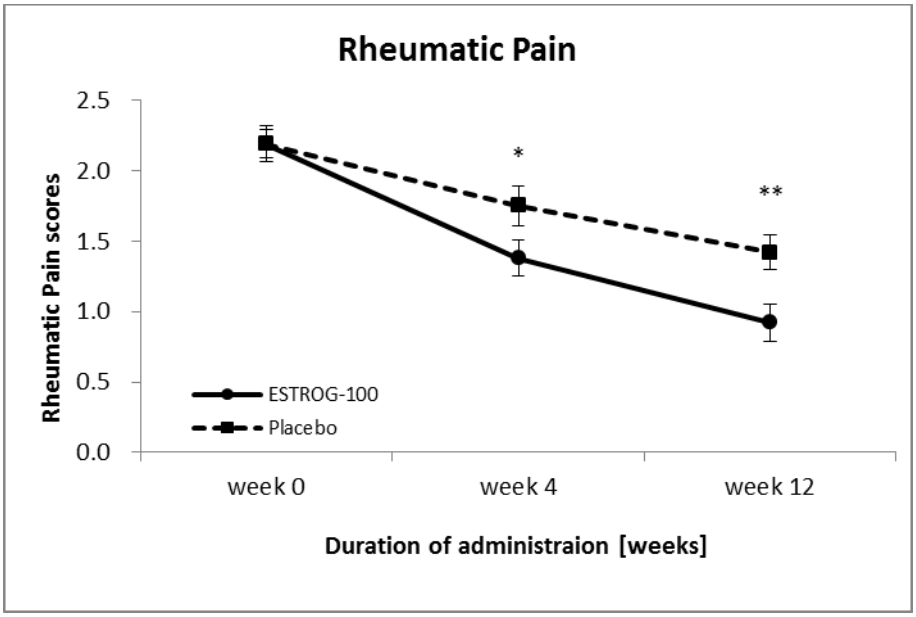


**Fig. 9. Changes of rheumatic pain (Mean±SE) during 12 weeks administration of EstroG-100 and placebo.**

SE: Standard Error, *: Statistically significant compared between groups; $p<0.05$ by t–test

**: Statistically significant compared between groups; $p<0.01$ by t–test

Table 6. Mean change in scores of the individual symptom of KMI (Headaches, Palpitation and Formication)

| | | EstroG-100 N=48 Mean±SD | Placebo N=48 Mean±SD |
|---|---|---|---|
| Headaches | Week 0 (Baseline) | 1.69±1.01 | 1.63±0.91 |
| | Week 4 | 1.00±0.85 | 1.10±0.99 |
| | Change from baseline | -0.69±0.99$^{\#\#}$ | -0.52±0.97$^{\#\#}$ |
| | Week 12 | 0.75±0.79 | 0.92±0.92 |
| | Change from baseline | -0.94±1.10$^{\#\#}$ | -0.71±1.03$^{\#\#}$ |
| Pounding of the heart (=palpitation) | Week 0 (Baseline) | 1.79±0.90 | 1.79±0.90 |
| | Week 4 | 1.10±0.81 | 1.19±0.94 |
| | Change from baseline | -0.69±0.95$^{\#\#}$ | -0.60±1.05$^{\#\#}$ |
| | Week 12 | 0.67±0.72 | 0.92±0.79 |

| | | | |
|---|---|---|---|
| | Change from baseline | -1.13±1.02## | -0.88±1.16## |
| Sensation of crawling on the skin (=formication) | Week 0 (Baseline) | 1.27±1.07 | 1.10±0.93 |
| | Week 4 | 0.65±0.81 | 0.81±0.87 |
| | Change from baseline | -0.63±1.10## | -0.29±1.05 |
| | Week 12 | 0.48±0.77 | 0.73±0.82 |
| | Change from baseline | -0.79±1.07*,## | -0.38±0.96## |

*, p<0.05 compared between groups by t-test
##, p<0.01 compared to baseline to baseline by paired t-test

The mean headaches score was significantly reduced in EstroG-100 group from 1.69±1.01 at baseline to 1.00±0.85 at week 4 and to 0.75±0.79 at week 12 (p<0.01) while that was also lowered from 1.63±0.91 at baseline to 1.10±0.99 at week 4 after and to 0.92±0.92 at week 12 in the placebo group (p<0.01).

The mean palpitation score was significantly reduced in EstroG-100 group from 1.79±0.90 at baseline to 1.10±0.81 at week 4 and to 0.67±0.72 at week 12 (p<0.01) while that was also lowered from 1.79±0.90 at baseline to 1.19±0.94 at week 4 after and to 0.92±0.79 at week 12 in the placebo group (p<0.01).

The mean formication (=sensation of crawling on the skin) score was significantly reduced in EstroG-100 group from 1.27±1.07 at baseline to 0.65±0.81 at week 4 and to 0.48±0.77 at week 12 (p<0.01). The improvement at week 12 (0.79±1.07 in the EstroG-100 group vs. 0.38±0.96 in the placebo group) was significant between the two groups (p<0.05). The improvement of formication is shown on Table 6 and Fig. 10.

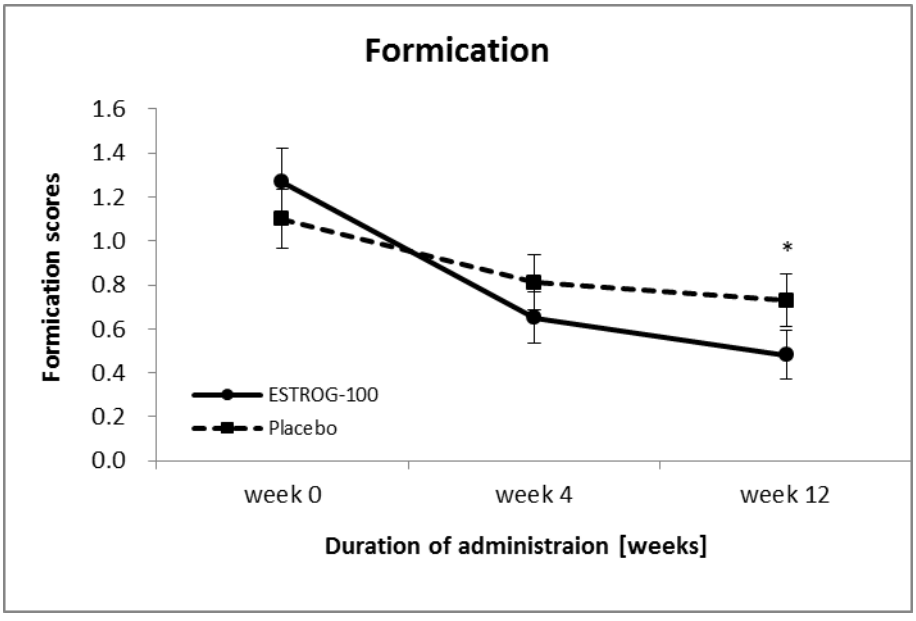


**Fig. 10. Changes of formication (Mean±SE) during 12 weeks administration of EstroG-100 and placebo.**
SE: Standard Error, *: Statistically significant compared between groups; p<0.05 by t–test

Significant improvement was found in the mean vaginal dryness (=sensation of dryness or burning in the vagina; difficulty with sexual intercourse) score. In EstroG-100 group showed improvement from 2.13±0.82 at baseline to 1.46±1.09 at week 4 and to 1.13±1.12 at week 12 ($p<0.01$). The difference in vaginal dryness score between the baseline and week 12 was 1.00±0.99 in the test group and 0.63±1.20 in the placebo group. The improvement between the two groups was statistically significant ($p<0.05$) (Table 7 and Fig. 11).

Table 7. Mean change in scores of vaginal dryness

| | EstroG-100<br>N=48<br>Mean±SD | Placebo<br>N=48<br>Mean±SD |
|---|---|---|
| Week0 (Baseline) | 2.13±0.82 | 2.04±0.90 |
| Week 4 | 1.46±1.09 | 1.48±1.11 |
| Change from baseline | -0.67±0.95$^{\#\#}$ | -0.56±1.13$^{\#\#}$ |
| Week 12 | 1.13±1.12 | 1.42±1.07 |
| Change from baseline | -1.00±0.99$^{*\ \#\#}$ | -0.63±1.20$^{\#\#}$ |

*, $p<0.05$ compared between groups by t-test
##, $p<0.01$ compared to baseline to baseline by paired t-test

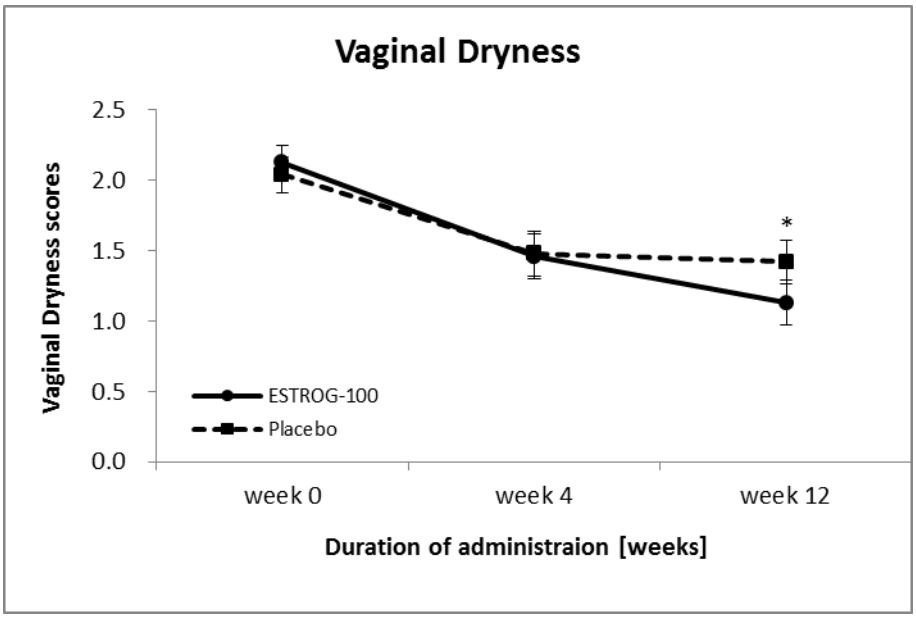


**Fig. 11. Changes of vaginal dryness (Mean±SE) during 12 weeks administration of EstroG-100 and placebo.**
SE: Standard Error, *: Statistically significant compared between groups; $p<0.05$ by t–test

8.4. Serum metabolic and safety

For the safety evaluation, among 105 enrolled participants, 104 participants who administered either EstroG-100 or placebo at least once were included in the evaluation. 54 participants were in the placebo group, and 50 participants in EstroG-100 group.

No statistically significant differences were observed between baseline and week 12 as well as between the treatment and placebo groups with regard to such biochemical markers as LDL, HDL, Total Cholesterol, Hemoglobin, Platelet, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Total Protein, Albumin, serum estrogen (E2), follicular stimulating hormone (FSH) and Endometrial Thickness ($p>0.05$). The changes in weight and the BMI were observed not to be significant in either the EstroG-100 or the placebo group after 12 weeks ($p>0.05$) as shown in Table 8.

Table 8. Change of the variables for 12 weeks of treatment with EstroG-100

| | EstroG-100 | | Placebo | |
|---|---|---|---|---|
| | Baseline | Week 12 | Baseline | Week 12 |
| LDL (mg/dL) | 129.72±34.43 | 127.40±36.29 | 125.69±33.75 | 122.89±29.38 |
| HDL (mg/dL) | 61.88±12.00 | 59.98±12.95 | 59.09±14.23 | 57.74±13.98 |
| T-Chol (mg/dL) | 212.44±36.83 | 207.58±34.76 | 203.67±34.91 | 198.39±32.49 |
| RBC ($10^6/\mu L$) | 4.43±0.29 | 4.41±0.29 | 4.34±0.27 | 4.30±0.24 |
| Hematocrit (%) | 40.19±2.51 | 40.07±2.62 | 39.23±2.59 | 39.14±2.41 |
| Hb (g/dL) | 13.54±0.83 | 13.42±0.81 | 13.24±0.97 | 13.11±0.94 |
| Platelet ($10^3/\mu L$) | 239.84±40.75 | 243.42±41.34 | 241.06±40.51 | 239.65±40.31 |
| ALT (IU/L) | 18.54±8.99 | 19.80±10.83 | 20.65±11.93 | 20.48±14.75 |
| AST (IU/L) | 22.70±5.32 | 23.36±7.14 | 24.44±8.35 | 24.20±12.63 |
| Protein (g/dL) | 7.19±0.41 | 7.19±0.34 | 7.20±0.36 | 7.12±0.36 |
| Albumin (g/dL) | 4.47±0.24 | 4.42±0.23 | 4.46±0.20 | 4.39±0.17 |
| E2 (Pg/ml) | 21.93±24.24 | 27.26±41.37 | 31.10±51.23 | 22.39±32.77 |
| FSH (mIU/ml) | 60.74±32.30 | 63.03±32.71 | 57.78±32.56 | 59.49±28.93 |
| Endometrial Thickness (mm) | 4.88±5.20 | 4.66±4.38 | 4.37±3.39 | 3.68±1.60 |
| Weight (kg) | 56.98±7.04 | 57.66±7.25 | 59.06±7.88 | 59.46±8.05 |

LDL, low density lipoprotein; HDL, high density lipoprotein; T-chol, Total cholesterol; RBC, red blood cell; WBC, White blood cell; Hb, Hemoglobin; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; T-protein, Total protein; E2, estradiol; FSH, follicular stimulating hormone

ALP and TG levels showed statistically significant increase in both groups at week 12 compared to baseline ($p<0.05$) while creatinine was significantly decreased in both EstorG-100 group and placebo ($p<0.05$). However, all of the mean values at baseline and week 12 were normal. WBC level was significantly increased compared to the baseline in treatment group ($p<0.01$). However, all of the

mean values at baseline and week 12 were well within the normal range. Though there was no significant difference in fasting glucose level at week 12 from that of the baseline in EstroG-100 group, there was a significant increase between the treatment and placebo groups ($p<0.05$) (Table 9). All of the mean values were normal.

Table 9. Change of the variables for 12 weeks of treatment with EstroG-100

| | EstroG-100 | | Placebo | | Total | | Typical Normal Range※ |
|---|---|---|---|---|---|---|---|
| | Pre-treatment | Post-treatment | Pre-treatment | Post-treatment | Pre-treatment | Post-treatment | |
| ALP (IU/L) | 60.32 ±16.82 | 64.40 ±18.86## | 64.76 ±20.07 | 67.70 ±19.84## | 62.63 ±18.63 | 66.12 ±19.35## | 44~147 |
| TG (mg/dL) | 95.98 ±37.13 | 115.46 ±59.43# | 107.93 ±65.66 | 129.17 ±101.00# | 102.08 ±54.05 | 122.47 ±83.62## | < 150.0 |
| Creatinine (mg/dL) | 0.73 ±0.14 | 0.70 ±0.11## | 0.74 ±0.13 | 0.71 ±0.11# | 0.74 ±0.13 | 0.70 ±0.11## | 0.6~1.1 |
| WBC ($10^3/\mu L$) | 5.86 ±1.23 | 6.31 ±1.30** ## | 6.07 ±1.34 | 5.86 ±1.21 | 5.97 ±1.29 | 6.07 ±1.26 | 4.5~10.0 |
| Fasting glucose (mg/dL) | 94.72 ±8.92 | 98.04 ±13.73* | 96.67 ±7.45 | 95.11 ±9.28 | 95.73 ±8.21 | 96.52 ±11.67 | 70~100 (70~125) |

*, $p<0.05$ compared between groups **, $p<0.01$ compared between groups by t-test

#, $p<0.05$ compared to baseline to baseline ##, $p<0.01$ compared to baseline to baseline by paired t-test

※ http://www.nlm.nih.gov/medlineplus/[1]

ALP, Alkaline phosphatase; TG, Triglyceride

8.5. Adverse events.

No severe adverse events were observed or reported by participants who received EstroG-100 in this study. There were 12 mild events out of 8 participants reported while 7 mild and 1 moderate adverse events reported in 6 patients. All 14 participants were not dropped out and finished this study to the end.

## 9. Discussion

Of the 122 participants screened, 105 participants met the screening criteria and were enrolled in to the study. For the safety evaluation, among 105 enrolled participants, 104 participants who administered either EstroG-100 or placebo at least once were included in the evaluation. The age of participants is 54.04±6.03 years and there was no statistical difference between two groups. The BMI were 23.11±2.72 $kg/m^2$ and there was no difference between two groups.

For efficacy evaluation, 9 participants were dropped from the study for the exclusion criteria. 48 participants were in the placebo group and 48 participants in EstroG-100 group.

The mean quality of life score (KMI) was significantly improved in EstroG-100 group (35.42±7.96 at baseline to 14.85±10.04 at week 12) compared to that of placebo group (33.25±7.78 at baseline to 19.85±10.37 at week 12 ($p<0.01$)).

The mean scores of hot flush, paresthesia, nervousness, melancholia, vertigo, formication and vaginal dryness of EstroG-100 group were significantly improved at week 12 in comparison to those of placebo group ($p<0.05$). Fatigue and rheumatic pain of EstroG-100 group was significantly improved in compared

to the placebo group ($p<0.01$). Insomnia of EstroG-100 group was marginally significantly improved in compared to the placebo group ($p=0.084$).

After 12 weeks of trial, body weight, BMI and blood pressure were not changed significantly from baseline and there were no difference between groups.

In the process of clinical trial, one subject withdrew agreement because of palpitation. However, it has been confirmed by the participants that palpitation was not related to the administration of the study samples.

During the clinical trial, there were 4 adverse events that were suspected to be possibly related to the study samples. In the EstroG-100 group, mild upper abdominal pain and breast pain were observed. In the placebo group, moderate hepatic enzymes and function abnormalities and mild dizziness were observed. However, the participants of all four cases continued the administration until the end of the study, and all the related symptoms disappeared in the study periods.

On the serum biochemical and hematological measurements, there were no statistically significant differences between the two groups on blood pressure, serum E2, triglyceride, total cholesterol, LDL and HDL. For the consideration of potential estrogenic activity, serum E2, FSH, and endometrial thickness were measured but no significant differences or changes were observed.

## 10. Conclusion

In this study, oral administration of EstroG-100 for 12 weeks statistically significantly improved the quality of life and such nine different symptoms as hot flush, paresthesia, nervousness, melancholia, vertigo, fatigue, rheumatic pain, formication, and vaginal dryness of pre-, peri-, post-menopausal women. No severe adverse events were reported with EstroG-100. Weight, biochemical markers as well as serum hormone levels along with endometrial thickness were not changed with statistical significance.

Along with past study results[2,3], EstroG-100 was found to be safe and effective herbal formula that can improve women's quality of life and various menopausal symptoms.

## References

1. http://www.nlm.nih.gov/medlineplus

2. Ki Ho Lee, Duck Ju Lee, Sang Man Kim, Sang Hyeun Je, Eun Ki Kim, Hae Seung Han, In Kwon Han, Evaluation of Effectiveness and Safety of Natural Plants Extract(Estromon® ) on Perimenopausal Women for 1 Year, J. Korea Soc. Menopause 2005: 11(1). 16-26

3. Albert Chang, Bo-Yeon Kwak, Kwontaek Yi, Jae Soo Kim, The Effect of Herbal Extract (EstroG-100) on Pre-, Peri- and Post-Menopausal Women: A Randomized Double-blind, Placebo-controlled Study, Phytother. Res. 2012(26): 510-516