CLINICAL STUDY DOCUMENT

STUDY PROTOCOL

Official Title: Estrogen Herbals

Brief Title: Hormone Estradiol Replacement Therapy Additional Herbals (WH)

Unique Protocol ID: Estrogen Herbals

NCT Number: NCT02618148

Document Date: November 17, 2015

1. BACKGROUND AND RATIONALE

Hormone Replacement Therapy (HRT) with estrogens is widely utilized to alleviate moderate-to-severe vasomotor symptoms, vulvovaginal atrophy, and to prevent osteoporosis in postmenopausal and perimenopausal women. However, conventional HRT is associated with a well-documented increase in the risk of venous thromboembolism (VTE), deep vein thrombosis (DVT), pulmonary embolism, and ischemic stroke.

This study investigates a novel therapeutic approach combining traditional Hormone Replacement Therapy (specifically Estradiol valerate and Progesterone) with a targeted herbal composite consisting of garlic oil, rutin, and nattokinase. Garlic oil exerts anti-platelet aggregation effects; rutin serves as a potent antioxidant to improve endothelial health; and nattokinase, a fibrinolytic enzyme derived from Bacillus subtilis natto, acts directly to degrade cross-linked fibrin and reduce blood viscosity. The primary rationale is to determine whether this combination therapy can mitigate the pro-thrombotic side effects of estrogen therapy, thereby improving the safety profile of HRT in symptomatic menopausal women.

2. STUDY OBJECTIVES

- Primary Objective: To evaluate the effect of adding a specific herbal combination (garlic oil, rutin, and nattokinase) to conventional HRT on serum estradiol profiles and related coagulation safety markers over a 12-to-24-month period.

- Secondary Objective: To assess the clinical tolerability, safety, and reduction of estrogen-mediated side effects in postmenopausal and perimenopausal patients.

3. STUDY DESIGN

- Study Type: Interventional

- Primary Purpose: Health Services Research

- Study Phase: Phase 4

- Interventional Study Model: Parallel Assignment

- Number of Arms: 2 Arms

- Allocation: Randomized

- Masking: Single-blind (Care Provider)

- Total Target Enrollment: 60 subjects (Actual enrollment completed: 60)

4. ELIGIBILITY CRITERIA

4.1 Inclusion Criteria:

- Female patients aged 35 to 65 years.

- Experiencing clinical symptoms of oestrogen deficiency in perimenopausal or postmenopausal states.

- Requiring Hormone Replacement Therapy (HRT) for symptomatic relief or for the prevention of osteoporosis in patients at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for osteoporosis prevention.

- Voluntarily signed the informed consent form.

4.2 Exclusion Criteria:

- Known, past, or suspected breast cancer.

- Known or suspected oestrogen-dependent malignant tumours (e.g., endometrial cancer).

- Undiagnosed genital bleeding.

- Untreated endometrial hyperplasia.

- Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism).

- Known thrombophilic disorders (e.g., protein C, protein S, or antithrombin deficiency).

- Active or recent arterial thromboembolic disease (e.g., angina, myocardial infarction).

- Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal.

- Known hypersensitivity to the active substances or to any of the excipients (including garlic, rutin, or nattokinase).

5. STUDY ARMS AND INTERVENTIONS

5.1 Arm 1: Experimental - ESTROGEN HERBALS 21

- Description: Targeted for menopausal women who wish to maintain monthly menstruation.

- Intervention: Drug - ESTROGEN HERBALS 21

  * 17β-estradiol: 1.5 mg orally every 24 hours for 21 consecutive days, followed by a 7-day treatment-free interval.

  * Progesterone: 5 mg orally every 24 hours for the final 10 days of the estradiol cycle, followed by a 7-day treatment-free interval.

  * Garlic oil: 30 mg orally every 24 hours for 28 consecutive days.

  * Enzyme Nattokinase: 300 FU orally every 24 hours for 28 consecutive days.

  * Other Name: EPGANA 21

5.2 Arm 2: Experimental - ESTROGEN HERBALS 28

- Description: Targeted for menopausal women who do not wish to maintain monthly menstruation.

- Intervention: Drug - ESTROGEN HERBALS 28

  * 17β-estradiol: 1.5 mg orally every 24 hours continuously for 28 days.

  * Garlic oil: 30 mg orally every 24 hours continuously for 28 days.

  * Enzyme Nattokinase: 300 FU orally every 24 hours continuously for 28 days.

  * Other Name: EPGANA 28

6. OUTCOME MEASURES

6.1 Primary Outcome Measure:

- Title: Time to Estradiol > 35 pg/ml

- Description: Measurement of serum estradiol levels via blood sampling to determine the physiological timeframe required to achieve a concentration greater than 35 pg/ml. Stratified analyses will be conducted for Group (A) Females premenopausal (Reference Range: 35-525 pg/ml) and Group (B) Females postmenopausal (Reference Range: 0-35 pg/ml).

- Time Frame: 1 year

6.2 Secondary Outcome Measure:

- Title: Time to Estradiol > 35 pg/ml / Side Effect Profile

- Description: Monitoring of prolonged hormonal stabilization and measurement of the time to maintain serum estradiol levels, with extended safety evaluation regarding pro-thrombotic markers and coagulation profiles.

- Time Frame: 2 years

7. ETHICAL OVERSIGHT

This study protocol was reviewed and formally approved by the National Institutes of Health - NCI - IRB #1 (Board Affiliation: US National Institutes of Health; Board Status: Approved; Approval Number: 17/11/2015). The study was conducted in strict accordance with the Declaration of Helsinki and local regulatory guidelines in Vietnam.