A Multi-center Clinical Study on the Efficacy and Safety of Kuntai Capsule Alone and in Combination With Hormones in the Treatment of Early-onset Hypoovarian Function

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Research Proposal Summary

Scheme number	HYKT18017S
Scheme name	A Multi-center Clinical Study on the Efficacy and Safety of Kuntai Capsule Alone and in Combination With Hormones in the Treatment of Early-onset Hypoovarian Function
Version number/date	Version 2.1 , June 18 , 2021
sponsor	Shanghai Haitian Pharmaceutical Technology Development Co., Ltd.
Clinical trial staging	Post-marketing clinical re-evaluation
test drug	Heyan Kuntai Capsules ®(Z20000083), each0.5g, was produced by Guiyang Xintian Pharmaceutical Co., Ltd.
Indications	POI (including subclinical stage)
Test purposes	To evaluate ®the efficacy and safety of Heyan Kuntai Capsules alone or in combination with hormone therapy in patients with POI (including subclinical stage) in improving ovarian function .
Research design	Prospective, multicenter, randomized, controlled clinical trial design
total number of cases	It is planned to complete 120 cases (considering the 20% dropout rate, at least 150 cases need to be enrolled)
number of research	6 _

centers	
Study period	24 months
research object	**Diagnostic criteria :** The diagnostic criteria for premature ovarian insufficiency (POI) refer to the "2017 Chinese Expert Consensus on Clinical Diagnosis and Treatment of Premature Ovarian Insufficiency" and "2016 Expert Consensus on Hormone Supplementation Therapy for Premature Ovarian Insufficiency"; including: (1) Age <40 years old; (2) oligomenorrhea or amenorrhea for at least 4 months; (3) at least 2 times serum basal follicle-stimulating hormone (FSH) > 25 IU/L (interval > 4 weeks). Subclinical POI: FSH level is 15~25 IU/L, which is a high-risk group. The diagnostic criteria for premature ovarian failure (POF) refer to the "2017 Chinese Expert Consensus on Clinical Diagnosis and Treatment of Premature Ovarian Insufficiency", which refers to amenorrhea, FSH>40IU/L, and decreased estrogen levels before the age of 40, accompanied by varying degrees of perimenopause Stage symptoms are the terminal stage of POI. **standard constrain:** 1. 18 years old ≤ age < 40 years old; 2. At least two (>4 weeks interval) basal FSH≥15IU/L, with or without oligomenorrhea or menopause. 3. Informed consent, voluntary experiment. **Exclusion criteria:** 1. pregnant and lactating patients; 2. Patients with endometriosis , adenomyosis , endometrial lesions (submucosal fibroids , endometrial polyps, etc.), uterine fibroids >4cm or hysterectomy ; 3. Patients with known or suspected history of breast cancer and estrogen-dependent malignancies; 4. a personal history of venous thromboembolism (VTE) or with a high risk of VTE (including body mass index > 30 kg/m ^{2} , smoking, family history of thrombophilia); 5. Porphyria patients; 6. Patients with serious primary diseases such as cardiovascular, liver, kidney, hematopoietic system or mental illness;

	7. Patients who are participating in other clinical trials or have participated in other clinical trials within the past three months; 8. Patients with suspected or real history of alcohol and drug abuse; 9. Known allergy to the investigational drug or its components; 10. Other patients deemed unsuitable for participation in this trial by the investigator. Note: Patients who were receiving hormone replacement therapy at the time of recruitment were required to take at least a 3 -month suspension of medication to participate in this trial.
Trial grouping and medication	**1 POI patient** According to the random sequence generated by computer, eligible patients were randomly assigned to Kuntai group , control group and combination group according to 1: 1 : 1 . (A) Kuntai group (30 cases): Oral Kuntai capsules, 4 capsules at a time, 3 times a day , 28 days as a course of treatment, taking medicine for 3 courses ; (B) Control group (30 cases): the sequential regimen of estrogen and progesterone was used, and the drug was estradiol tablets/estradiol dydrogesterone tablets (fenmetone), and red tablets (estradiol, 2 mg/d), and gray tablets (estradiol , 2 mg/d, dydrogesterone, 10 mg/d) were taken for the next 14 days , 28 days as a course of treatment, and three courses of medication were taken. (C) Combination group (30 cases): On the basis of hormone therapy, Kuntai Capsules were added, and the dose was the same as that of Kuntai group and hormone group for 3 months. **2. Patients with POI in subclinical stage** : self-control before and after experiment group (30 cases): Oral Kuntai capsules, 4 capsules at a time , 3 times a day, 28 days as a course of treatment, taking medicine for 3 courses of treatment.
Treatment and follow-up	1.Course of treatment: 28 days as a course of treatment, taking medicine for 3 courses of treatment 2. Visit points: before treatment (stage V_0 , screening period, days -35 to 0), baseline period (day 0), after 3 months of treatment (stage V_1 , days 84 to 105), drug withdrawal 3 months later (V_2 stage , 168-210 days) and 6 months after drug withdrawal (V_3 stage , 252-315 days) . Specific inspection items include: 1. The patient 's hormone levels (basal FSH, LH, E_2) were detected in V_0 , V_1 , and V_2 stages ; 2 Anti-Müllerian hormone (AMH) was detected in patients at V 0 and V 1 stages ; 3 The patients underwent B-ultrasound at V 0 and V 1 stage to monitor the follicular development ,

	record the number of antral follicles (AFC), ovarian hemodynamic parameters (PSV, EDV, S/D, RI and PI); 4. Modified Kupperman score was performed in V_0 , V_1 and V_2 stage; 5 Pregnancy was recorded at the V_2 outpatient follow-up for patients with reproductive needs ; 6 patients at V_0 and V_1 to detect blood routine (RBC, WBC, PLT, HGB) , liver function (ALT, AST) and renal function (BUN, Cr) , and recorded adverse events. Note: 1 Basal follicle-stimulating hormone (FSH) ≥ 15IU/L at first visit in patient V0 , and if other inclusion criteria are met, if the patient has a history of testing with a baseline FSH ≥ 15 IU/L in the past (interval> 4 weeks) , he or she can be included in this study and drug therapy can be started; (Interval > 4 weeks) If the basic FSH ≥ 15 IU/L has not been diagnosed , the patient is required to visit the hospital again after 4 weeks. If the basic FSH is still ≥ 15 IU/L , they can be included in this study and drug therapy can be started. 2 For patients with regular menstrual periods, the basal FSH and antral follicle count (AFC) should be followed up on the 2nd to 4th day of the menstrual cycle. If the patient has menstrual cramps after the follow-up and has not exceeded the visit window, they are required to re-examine on the 2nd to 4th day of the menstrual cycle and record the examination data.
study endpoint	Primary endpoint : FSH, modified Kupperman score Secondary endpoints : (1) FSH/LH, LH , E_2 ; (2) Antral follicle count (AFC); (3) Anti- Müllerian hormone (AMH); (4) Proportion of patients with normal menstruation; (5) Ovarian hemodynamics parameters (PSV, EDV, S/D, RI and PI); (6) Clinical pregnancy rate (patients with reproductive needs).
security indicators	1 Blood routine (RBC, WBC, PLT, HGB) , liver function (ALT, AST) and renal function (BUN, Cr) ; 2 Patient adverse events were recorded.