RESEARCH PROPOSAL

Version – 1.0
Date – 11 Aug 2026
Organization's Unique Protocol ID: hkuszh2026127
Other Identifier: IRB[2026]204

1. General Information

Title:

A Randomized, Double-Blind, Placebo-Controlled Trial of finerenone in women with premature ovarian insufficiency

2. Background

Premature ovarian insufficiency (POI) represents a major challenge in the field of reproductive medicine. POI is characterized by the depletion or dysfunction of ovarian follicles before the age of 40, leading to menstrual irregularities, hypoestrogenism, elevated gonadotropin levels, and infertility[1]. It is defined as oligomenorrhea or amenorrhea lasting for at least four months, in conjunction with elevated serum follicle stimulating hormone (FSH) levels exceeding 25 IU/L in women under the age of 40[2].

Recent epidemiological studies estimate a global prevalence of approximately 3–4%, with a rising trend over the past two decades[3]. Although some POI patients may retain residual small follicles and intermittent ovarian activity, spontaneous ovulation and natural conception remain rare and unpredictable. Furthermore, the overall reproductive potential of women with POI is markedly reduced, resulting in very low live birth rates[4].

Currently, therapeutic options for POI remain limited. Hormone replacement therapy (HRT) is primarily used to alleviate hypoestrogenic symptoms and to prevent long-term sequelae associated with estrogen deficiency. However, it does not restore ovarian function or improve fertility outcomes. Emerging approaches, including intra-ovarian injection of umbilical-cord-derived mesenchymal stem cells (UC-MSCs) and the application of hypoxia-preconditioned MSC-derived exosomes (HExos), have shown preliminary potential in experimental or early-phase studies, but remain investigational and lack robust clinical evidence [5,6]. At present, oocyte donation remains the only effective option for achieving pregnancy in women with POI, although its application is limited by cultural, ethical, and psychological considerations. Therefore, there is an urgent need to explore novel pharmacological strategies aimed at activating or preserving residual follicular activity in POI, with the goal of improving reproductive outcomes.

Finerenone is a next-generation, non-steroidal and highly selective mineralocorticoid receptor (MR) antagonist[7], originally developed for its renal and cardiovascular protective properties and now approved for the treatment of chronic kidney disease in patients with type 2 diabetes[8-10].Beyond its established indications, our recent preclinical and early clinical studies have suggested that Finerenone may exert beneficial effects on ovarian physiology. In mouse models, administration of Finerenone facilitated the activation and growth of residual small follicles without compromising oocyte quality, embryo development, or offspring health. Consistent with these findings, our pilot clinical study in women with POI reported that intermittent oral Finerenone administration (20 mg twice weekly) promoted antral follicle emergence and enabled the retrieval of mature metaphase II oocytes and viable embryos. Mechanistic studies using single-cell transcriptomics further demonstrated that Finerenone alleviates ovarian stromal fibrosis and attenuates extracellular matrix–mediated inhibitory signaling to granulosa cells, thereby creating a more permissive microenvironment for follicle growth [11]. Despite these encouraging preliminary findings, prospective clinical studies evaluating Finerenone in women with POI are still limited, leaving a critical gap in evidence regarding its therapeutic potential in reproductive medicine.

The present randomized trial aims to evaluate the efficacy of Finerenone in improving ovarian reserve and follicle development among women with POI. The hypothesis is that Finerenone can improve ovarian reserve, stimulate follicle activation, leading to ovulation and potentially enabling natural conception or follicle development for oocyte retrieval in in vitro fertilization.

This trial is innovative in introducing a novel, repurposed non-steroidal mineralocorticoid receptor antagonist into the field of reproductive medicine, where treatment options for POI remain extremely limited. It not only addresses a critical gap in current infertility management but also holds the potential to establish a new therapeutic strategy that could significantly improve the prognosis and quality of life for affected women.

References:

1. Drakopoulos, P., et al., *Update on the management of poor ovarian response in IVF: the shift from Bologna criteria to the Poseidon concept.* Ther Adv Reprod Health, 2020. **14**: p. 2633494120941480.
2. European Society for Human, R., et al., *ESHRE Guideline: management of women with premature ovarian insufficiency.* Hum Reprod, 2016. **31**(5): p. 926-37.
3. De Vos, M., P. Devroey, and B.C. Fauser, *Primary ovarian insufficiency.* Lancet, 2010. **376**(9744): p. 911-21.
4. Nash, Z. and M. Davies, *Premature ovarian insufficiency.* BMJ, 2024. **384**: p. e077469.
5. Zhang, S., et al., *Exosomes derived from hypoxic mesenchymal stem cell ameliorate premature ovarian insufficiency by reducing mitochondrial oxidative stress.* Sci Rep, 2025. **15**(1): p. 8235.
6. Yan, L., et al., *Clinical analysis of human umbilical cord mesenchymal stem cell allotransplantation in patients with premature ovarian insufficiency.* Cell Prolif, 2020. **53**(12): p. e12938.
7. Kintscher, U., G.L. Bakris, and P. Kolkhof, *Novel non-steroidal mineralocorticoid receptor antagonists in cardiorenal disease.* Br J Pharmacol, 2022. **179**(13): p. 3220-3234.
8. Pei, H., et al., *The use of a novel non-steroidal mineralocorticoid receptor antagonist finerenone for the treatment of chronic heart failure: A systematic review and meta-analysis.* Medicine (Baltimore), 2018. **97**(16): p. e0254.
9. Lerma, E.V. and D.J. Wilson, *Finerenone: a mineralocorticoid receptor antagonist for the treatment of chronic kidney disease associated with type 2 diabetes.* Expert Rev Clin Pharmacol, 2022. **15**(5): p. 501-513.
10. Agarwal, R., et al., *Investigating new treatment opportunities for patients with chronic kidney disease in type 2 diabetes: the role of finerenone.* Nephrol Dial Transplant, 2022. **37**(6): p. 1014-1023.
11. Lin, Z., et al., A*ntifibrotic drug finerenone restores fertility in premature ovarian insufficiency*. Science, 2026. **391**(6785): p. eadz4075.

3. Objectives and hypotheses:

Primary Objective: To determine whether Finerenone treatment can increase the proportion of women with POI who are able to have oocytes aspirated during IVF within 24 weeks of Finerenone treatment.

Secondary Objectives:

- To determine whether finerenone treatment can improve ovarian reserve, as measured by antral follicle count (AFC) and serum anti-Mullerian hormone (AMH) levels.

Hypothesis: Finerenone improves the ovarian response, as reflected by an increased proportion of cycles with oocytes aspirated during IVF treatment in women with POI

4. Trial design:

A randomized, double-blind, placebo-controlled trial.

5. Subject selection and exclusion

5.1 Inclusion criteria:

Participants must meet all the following criteria:

i) Age of women <40 years.
ii) Diagnosis of POI according to ESHRE 2024 guidelines, defined as:
   - Oligomenorrhea or amenorrhea for at least 4 months; and
   - Elevated FSH levels (≥25mIU/ml) on a single measurement.

5.2 Exclusion criteria:

i) Known hypersensitivity to Finerenone or any of its excipients.
ii) Severe uncontrolled systemic diseases (cardiovascular, hepatic, renal, or endocrine disorders) that may interfere with study participation.
iii) Active malignancy or history of hormone-dependent cancer.
iv) Currently participating in another interventional trial.
v) Known chromosomal abnormalities or clinically significant genetic syndromes associated with POI.

6. Randomization and blinding

Participants will be randomly assigned in a 1:1 ratio to the finerenone group or placebo group. The random allocation sequence will be generated by an independent biostatistician using a computer-based random number generator.

Allocation concealment will be ensured using a centralized, password-protected randomization system that implements the pre-generated allocation sequence. Study investigators responsible for recruitment and clinical assessment will not have access to the allocation sequence. After eligibility confirmation and enrollment, treatment assignment will be obtained through the secure system, which will reveal the allocation only after participant registration.

7. Treatment of subjects

Participants would not be asked to pay for the drug or any extra procedure by participating in this study.

Counselling and Consent

Eligible women will be recruited for the study only after informed written consent is obtained. This consent will be provided after extensive counseling, which is distinct from routine clinical procedures. During this session, participants will be informed about:

- The purpose, objectives, and procedures of the study.
- The investigational nature of the treatments (Finerenone).
- Potential risks, benefits, and their rights as study participants.
- Confidentiality of their data and the option to withdraw at any time.

Participants taking hormonal replacement therapy will be asked to stop hormone replacement treatment at least 4 weeks prior to baseline evaluation to allow accurate assessment of spontaneous ovarian activity and hormone profile.

Participants will be randomly assigned to the Intervention group and the control group in 1:1 ratio. The randomization list will be prepared by a dedicated research nurse who will not be involved in this trial. The participants, researchers and the doctors taking care of the participants will be blinded to the group assignment.

Finerenone / placebo administration

Participants in the intervention group will receive Finerenone 20 mg orally, twice per week, for a total duration of 24 weeks. Participants will be counseled to take the study medication on the same days each week (e.g., every Monday and Thursday) to maintain consistency. A treatment diary will be provided, and pill counts will be performed at each follow-up visit to monitor adherence.
Participants in the control group will receive placebo orally twice per week for a total duration of 24 weeks. The placebo looks same as the intervention drug.

Follow-up and IVF treatment protocol

Participants will attend follow-up visits every 4 weeks, during which clinical assessment, ultrasound examination for AFC and serum AMH / FSH measurement will be performed. If an increase in AFC compared with the individual baseline value is observed, ultrasound monitoring will be performed weekly for four consecutive weeks. During this period, if follicular development is observed, participants can opt for ovarian stimulation for oocyte freezing in unmarried women or embryo freezing in married women. Natural cycle, mild stimulation, low dose FSH ovarian stimulation can be used at the discretion of the physicians or according to the standard protocol of the centre. Ovarian stimulation, ovulation trigger, oocyte retrieval, and laboratory procedures (including fertilization method and embryo cryopreservation) will be performed in accordance with local standard practice and clinical indications. Oocyte maturation assessment, fertilization outcomes, and embryo development will be recorded as per standard embryology laboratory procedures. Pregnancy outcomes will be followed up in participants undergoing embryo transfer, with pregnancy testing and ultrasound confirmation performed according to routine clinical practice. Ongoing pregnancy and delivery outcomes will be recorded where applicable.

8. Study outcomes

The primary outcome is the proportion of POI women with oocytes aspirated during IVF.

Secondary outcomes include
1) Ovarian response markers
- AFC
- AMH
- Serum estradiol (E2) level on trigger day during follicular development

2) IVF laboratory outcomes
- Number of total and mature oocytes
- Fertilization rate
- Number of embryos formed
- Blastocyst development rate / high-quality embryo rate

3) Clinical outcomes (IVF cycle derived only)
- Clinical pregnancy rate (ultrasound-confirmed intrauterine gestational sac at ~6–7 weeks)
- Ongoing pregnancy rate (fetal cardiac activity at 8–10 weeks)
- Live birth rate (delivery ≥24 weeks gestation)
- Miscarriage rate

9. Statistics

9.1 Sample size

According to previous study [11], the proportion of women with oocytes aspirated was 5%. If we target the proportion after treatment increases to 50%, a total of 32 patients (i.e. 16 women in each group) will be required to have a 90% chance of detecting, as significant at the 5% level. Assume the dropout rate of 30%, a total of 46 women (i.e. 23 women per group) will be required.

9.2 Statistical tests:

Data will be presented as mean ± SD or median (IQR) for continuous variables, while categorical variables will be presented as counts and percentages. The primary outcome between groups will be compared using chi-squared test or Fisher's exact test as appropriate, together with odds ratio and a 95% confidence interval between groups. For secondary outcomes, continuous variables, such as AFC, serum AMH, and E2 levels, their changes from baseline to the end of the study will be assessed using linear mixed models adjusting for baseline values, depending on data distribution. Changes on continuous variables from baseline between group will be compared using student t-test or Mann-Whitney U test as appropriate, with Bonferroni adjustment. Logistic regression or other appropriate models may be applied to explore potential predictors of IVF clinical pregnancy, including age and BMI. A two-sided p-value < 0.05 will be considered statistically significant.

10. Assessment of safety

Safety will be assessed throughout the study period. Adverse events (AEs) and serious adverse events (SAEs) will be monitored and recorded at each study visit and whenever reported by participants. Particular attention will be paid to potential drug-related events associated with finerenone, including changes in renal function, electrolyte disturbances (especially hyperkalemia and hyponatremia), and cardiovascular parameters. In accordance with the prescribing information of finerenone, serum creatinine, estimated glomerular filtration rate (eGFR), and serum electrolytes (sodium and potassium) will be measured at baseline and every four weeks during treatment.

For participants who subsequently achieve IVF-related clinical pregnancy following embryo transfer, maternal and fetal outcomes will be followed until delivery, with particular attention to early pregnancy loss and congenital anomalies.

11. Direct access to source data / documents:

Trial-related monitoring, audits, IRB review and regulatory inspections are allowed.

12. Quality control and quality assurance

Recruited women will be managed by doctors, nurses and laboratory staff qualified in providing IVF treatment.

13. Ethics:

Written consent will be obtained from all patients. The patient information sheet and consent forms in English and Chinese are enclosed. Ethics approval will be obtained from the Institutional Review Board of The University of Hong Kong / Hospital Authority Hong Kong West Cluster.

14. Data Handling and record keeping

All data will be stored for three years. A designated research nurse will be responsible for data management including data coding, monitoring and verification. Investigators, research assistants, related healthcare providers will have access to the personal and study data during and after the study. The personal and study data after completion of 3 years storage period will be destroyed.

15. Financing and insurance

Both internal and external funding are being applied.

16. Publication policy

The findings of this study will be submitted for consideration for publication in a peer-reviewed scientific journal.

17. Supplements

The study will be conducted in compliance with the Declaration of Helsinki and Good Clinical Practice (ICH-GCP)

We certify that the information given is complete and accurate to the best of our knowledge.