Comparison of Crinone® versus combination medication for luteal phase support on the ongoing pregnancy rate of frozen-thawed cycle in Chinese population a randomized, interventional, open-label, Phase IV, single center, pilot study

Title Page

Clinical Study Protocol Title:	Comparison of Crinone® versus combination medication for luteal phase support on the ongoing pregnancy rate of frozen-thawed cycle in Chinese population: a randomized, interventional, open-label, Phase IV, single center, pilot study
Study Number:	MS200113_0005
Amendment Number	2
Merck Compound Number:	Not applicable
Short Title:	ACCESS
Principal Investigator:	PPD PPD
Sponsor Name and Legal Registered Address:	Merck Serono Co., Ltd., Beijing, China. Medical Responsible: Name: PPD Address: 23F Nuo Center, No. A2 Jiangtai Road, Chaoyang District, Beijing 100016, China Phone: PPD Fax: PPD email: PPD
Sponsor Legal Representative in the European Union:	Merck Healthcare KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany
Regulatory Agency Identifying Numbers:	Not applicable
Protocol Version:	19Jan2021/ Version 2.0-CHN
Replaces Version:	1Jul2020/ Version 1.2-CHN
Approval Date:	

Medical Monitor Name and Contact Information:	Name: PPD Company: PPD Address: PPD Phone: PPD email: PPD

Protocol Amendment and Summary of Changes

Type	Scope	Version Number	Notes
Original protocol	Country- or area-specific (China)	1.0	Initial version submitted to the first IRB or IEC
1st country-specific amendment to the original protocol	Country- or area-specific	1.1-CHN	Non-global amendments.
2nd country-specific amendment to the original protocol	Country- or area-specific	1.2-CHN	Non-global amendments.
3rd country-specific amendment to the original protocol	Country- or area-specific	2.0-CHN	Non-global amendments.

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	10 Oct 2018
1.1-CHN	1st country-specific amendment to the original protocol	15 Jan 2020
1.2-CHN	2nd country-specific amendment to the original protocol	1 Jul 2020
2.0-CHN	3rd country-specific amendment to the original protocol	19 Jan 2021

Protocol Version 1.1-CHN (15-Jan-2020)

Overall Rationale for Amendment

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, 1.2 Schema, 4.1 Overall Design, and 4.2 Scientific Rationale for Study Design	Study duration increased from 15 to 25 months	Study duration lengthened due to recruitment status and to accommodate protocol amendment finalization time
1.2 Schema, 4.1 Overall Design, Appendix 4 Visit Procedures	Remove visit 2 – estradiol valerate initiation Inclusion/Exclusion (I/E) criteria checking at visit 2 and 3 as well	Eligible patients for the study may have already started on estradiol valerate so by removing the estradiol valerate initiation procedure, it may improve patient enrollment
1.3 Schedule of Actitvities and Appendix 4	Removed visit 2 – estradiol valerate initiation and its administration and shifted all subsequent visits from 3 to 2 etc. Checking of I/E criteria added to visit 2 and 3 as well	Eligible patients for the study may have already started on estradiol valerate so by removing estradiol valerate initiation may improve patient enrollment
1.3 Schedule of Actitvities	Note for Duphaston® revised from dispensed to prescribed	The drug is prescribed by the Investigator and purchased by the patients themselves
4.1 Overall Design	Study period changed from 95 to 75 days	Duration of study changed after removing estradiol valerate initiation
5.1 Inclusion Criteria	Day of embryo now also includes Day 6 embryos	The outcomes are similar with Day 5 embryos transfer.
6.4 Study Intervention Compliance	Compliance is at a minimun of 80% not 80-85%.	This should not be a range.
6.5.1 Rescue Medicine	Definition for rescue medicine provided	Rescue medicine section was not clear enough and Investigators may confuse this with prohibited medicines. Therefore, a definition is now provided.
6.5.3 Prohibited Medicines	Clarified prohibited medicines. Participants are allowed to remain on study if both the Sponsor and the Investigator agrees with it. Rescue medicines are not considered prohibited medicines	Progestogens are usually used as rescue medicines.
6.5.4 Other Interventions	Procedure for estradiol valerate use now follows local practice. Original details removed.	Following local practice is easier to implement for Investigators

Section # and Name	Description of Change	Brief Rationale
8.3.1 8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	The AE reporting period for safety surveillance begins upon endometrial transformation instead of estradiol valerate initation.	Change due to removal of estradiol valerate initiation
8.4 Study intervention Overdose	Rescue medicines that are administered are not considered overdosing.	Routine clinical practice. Prevent protocol deviations.
Appendix 3	Paper serious adverse event (SAE) reporting methods revised	Currently, all SAEs and overdose must be recorded on the SAE report form as the primary reporting method, rather than the back-up method
Appendix 4 Visit Procedures Visit 1 (baseline evaluation)	Medical history prior to informed consent form (ICF) signing may also be accepted per the Investigator's discretion for the following: • -clinical and gynecological exam • -ultrasound • -serum human chorionic gonadotrophin (β-hCG) levels	Patients will have clinical and gynecological exams at their first visit in the clinic; exams will not repeat afterwards according to local practice. The patients' ultrasounds are usually performed at the clinic shortly prior to the signing of the ICF according to local practice. Therefore, there is no need to repeat the ultrasound after ICF signing. Serum β-hCG levels will be performed at the patient's first visit to the clinic; exams will not repeated afterwards according to local practice.
Appendix 4 Visit Procedures Visit 2 (endometrial transformation day)	Irrelevant wording for estradiol valerate removed and that related to its dose adjustment to reach appropriate endometrial thickness Added data to be collected for estradiol valerate including date of initiation, initial dose, details of dose adjustment, and duration and total dose. Endometrial thickness may be measured by ultrasound or if ultrasound was performed on the endometrial transformation day prior to signing the ICF, a new ultrasound is not required.	Due to changes in the study procedure, estradiol valerate is no longer considered an intervention; therefore all estradiol valerate-associated procedures have been removed. Due to the change in study procedure, data for estradiol valerate including date of initiation, initial dose, details of dose adjustment, and duration and total dose, will be collected at visit 2.
Appendix 4 Visit Procedures Visit 3 (embryo transfer day)	Days for assisted secretory transformation of the endometrium changed to 4-6 instead of just 4. Embryo allowed to be transferred include D5 and D6 instead of just D6 Embryo transfer may occur on the fifth, sixth, or seventh day instead of just the fifth. Ultrasound to assess the endometrium removed	Procedural changes described now follow that of local practice and does not affect the outcome of the study.

Section # and Name	Description of Change	Brief Rationale
Throughout	Minor editorial and document formatting revisions	Minor, therefore, have not been summarized

Protocol Version 1.2-CHN (1-Jul-2020)

Overall Rationale for Amendment

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	To add one more exclusion critieria: Participants with potential risk (The participants/parterner are from high risk region which can be tracked by health barcode) or symptoms of COVID-19 (eg. fever, cough etc).	To exclude subjects with potential COVID-19 risks

Protocol Version 2.0-CHN (19-Jan-2021)

Overall Rationale for Amendment

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Day of embryo now includes Day 5 embryos only.	According to the quality control data of all the FET blastocyst transfer (n = 110), there is a difference between CPR of D5 embryo transfer and D6 embryo transfer (61.8% vs. 43.3%). Only D5 embryo is allowed to be transferred is to reduce the bias produced by the day of transfer.
Appendix 4 Visit Procedures Visit 3 (embryo transfer day)	Only D5 embryo allowed to be transferred instead of both D5 and D6 embryo allowed to be transferred.	To reduce the bias produced by the day of transfer.

Table of Contents

1 Protocol Summary

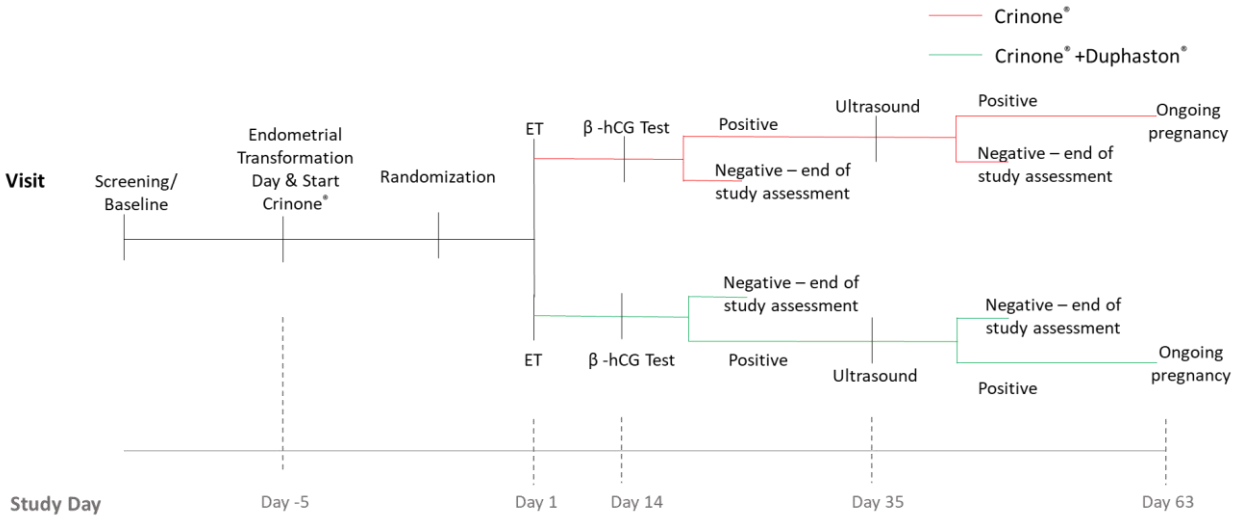
1.1 Synopsis

Protocol Title:	Comparison of Crinone® versus combination medication for luteal phase support on the ongoing pregnancy rate of frozen-thawed cycle in Chinese population: a randomized, interventional, open-label, Phase IV, single center, pilot study
Short Title:	ACCESS
Rationale:	Currently, oral progesterone combined with vaginal progesterone is the preferred regimen for luteal phase support in frozen-thawed embryo transfer (FET) cycles in China. It was reported that the clinical pregnancy rate of combined medication in FET-artificial cycles (AC) was 40% in a Chinese population, and a few Chinese retrospective studies supported the daily use of 90 mg of Crinone® during FET cycles. Therefore, in this pilot study, Crinone® (on its own) will be compared with combination medication (Crinone® plus Duphaston®) for luteal phase support in frozen thawed cycles by assessing their effects on the ongoing pregnancy rate; this study will provide preliminary evidence that differentiates the two protocols.
Objectives	**Endpoints (Outcome Measures)**
Primary	
To investigate the ongoing pregnancy rate of Crinone® compared to Crinone® in combination with Duphaston® during artificial FET cycles in Chinese population.	Ongoing pregnancy (at 10-12 weeks of pregnancy [8-10 weeks after ET]).
Secondary	
To evaluate the efficacy of Crinone® compared to Crinone® in combination with Duphaston® for luteal phase support in artificial FET cycles.	• β-hCG positive • Implantation • Clinical pregnancy

To evaluate the safety of Crinone® compared to Crinone® in combination with Duphaston® for luteal phase support in artificial FET cycles.	• Early abortion • Bleeding (luteal phase, vaginal) • The safety profile of the study intervention will be assessed according to Section 8.2.
Overall Design:	This is a local, single center, open label, pilot, randomized controlled clinical study to compare the efficacy and safety of Crinone® versus combination medication.
Number of Participants	CCI
Study Intervention (Crinone® and combination) Groups and Duration	The study participants are those who receive FET in ACs. This study plans on including 334 participants from a single reproductive center over 25 months.
Involvement of Special Committee(s):	No

1.2 Schema

This is a local, single center, open label, pilot, randomized controlled clinical study to compare the efficacy and safety of Crinone® versus combination medication. The study participants are those who will receive frozen-thawed embryo transfer (FET) in artificial cycles (ACs). This study plans on including 334 participants from a single reproductive center over 25 months.



The participants will sign an ICF; the participants are free to withdraw at any time without prejudice to their medical care, and they are not obliged to state their reasons for withdrawal. Participants will be randomized on the day of embryo transfer (ET). Upon site initiation, the Investigator site will enroll the eligible participants who meet the inclusion and none of the exclusion criteria in a consecutive manner until the enrollment target is reached. Relevant data according to study requirements will be recorded in a standard case report forms (CRF). When the study starts, this reproductive center will include participants who enter the cycle. The information of the qualified yet excluded participants who have signed ICFs will be recorded, and the reason for their exclusion will also be recorded in the CRF. If a participant has entered the study and later discontinue their study intervention, the reason for discontinuing the study intervention will be recorded in the CRF.

Participant follow-up will occur until her ongoing pregnancy is confirmed and/or until End of Study (defined in Section 4.4)

1.3 Schedule of Activities

Visit	Screening/ Baseline	Endometrial Transformation Day	Embryo Transfer (ET) Day (see Appendix 4 Visit 3)	β -hCG Test	Clinical Pregnancy Assessment	Ongoing Pregnancy Assessment	Notes
Study Day		**Day -5**	**Day 1**	**Day 14**	**Day 35**	**Day 63**	Ongoing pregnancy assessment occurs between 10-12 weeks of pregnancy (8-10 weeks after ET). The middle number of 9 weeks (Day 63) after ET is used to define the study day with a window of 10 days on each side as leeway
Window (day)		**±1**	**0**	**±1**	**±7**	**±10**	
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	
Signed ICF	×						
Randomization			×				
Demography	×						
Medical history	×						
Inclusion and exclusion criteria	×	×	×				
Physical examination and vital signs	×						
Weight and height	×						
Clinical and gynecological examination	×						
Ultrasound	× (see Appendix 4 Visit 1)	× (see Appendix 4 Visit 2)					Visit 2: If the ultrasound was performed on the endometrial transformation day prior to signing the ICF, a new ultrasound is not required.
Serum β-hCG levels	×			×			
Administration of Crinone®		< ---------- >					Crinone® will be dispensed at each scheduled visit starting from the endometrial transformation day. Crinone®

							should be dispensed with enough amount for self-administration until the next scheduled visit.
Administration of Duphaston® (combination medication group)			< ---------- >				Duphaston® will be prescribed at each scheduled visit starting from the ET day. Duphaston® should be dispensed with enough amount for self-administration until the next scheduled visit.
ET			×				
Clinical pregnancy as assessed by ultrasound scan					×		
Ongoing pregnancy assessment						×	
AEs		×	×	×	×	×	
Bleeding assessment				×	×	×	Bleeding assessment on Visit 5 will include luteal phase bleeding; the ones on Visits 6 will include vaginal bleeding.
Concomitant medication	×	×	×	×	×	×	

2 Introduction

Progesterone plays an important role in endometrial-embryo synchrony and the maintenance of early pregnancy. Crinone® (an intravaginal progesterone gel) and Duphaston® (an oral progesterone tablet) are used during frozen-thawed embryo transfer (FET) cycles for luteal phase support. This study investigates the ongoing pregnancy rate of Crinone® versus Crinone® in combination with Duphaston® during artificial FET cycles in a healthy Chinese population.

Complete information on the chemistry, pharmacology, efficacy, and safety of Crinone® is in the package insert.**Study Rationale**

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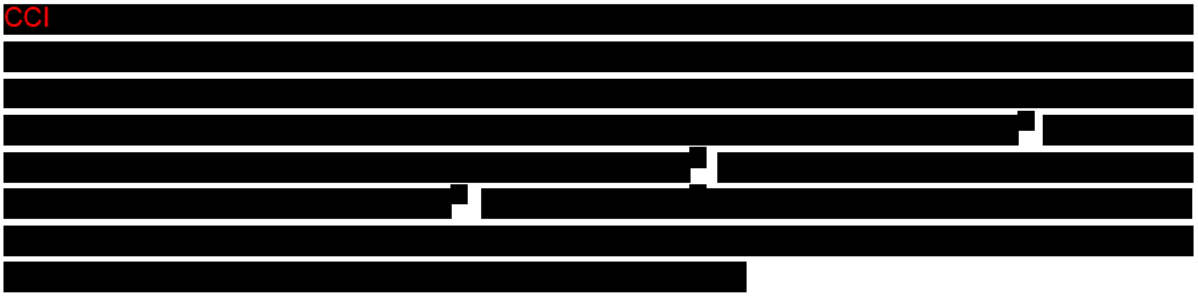

2.2 Background

The number of FET cycles has increased in modern assisted reproductive treatment (ART) since its first success in clinical pregnancy by Trounson et al in Australia in 1983 (7,8).

There are several reasons leading to the increased use of FET cycles, one of which is the deleterious effect of controlled ovarian stimulation on endometrial receptivity. Thus, an adequately prepared endometrium during a FET transfer cycle to improve pregnancy rates is essential (9–12). Elective transfer of frozen embryos reduces the risk of ovarian hyperstimulation syndrome and multiple pregnancies. Therefore, surplus embryos are cryopreserved. Evidence indicated that clinical pregnancy rates of in vitro fertilization (IVF) were the same in women using both fresh and FET cycles (13). Hence, this paradigm shift has resulted in an overall increase in the number of FET cycles in current reproductive medicine practices (14). Today, at least 25% of ART births are the result of FET (14).

The factors associated with successful FET include clinical medication regimen, embryo quality, and synchronization between embryos and the endometrium. The regimen for how the endometrium is prepared is essential. Current medication regimens clinically used for endometrial preparation include the natural cycle, hormone replacement therapy (the AC), and the ovarian stimulation cycle. Monitoring during the natural cycle regimen aims to determine embryo recovery and transfer time; this process generally requires continuous monitoring and the cycle could be cancelled when abnormal follicles develop. The regimen for ovarian stimulation cycle involves artificially generating high hormone levels in the body, which leads to an earlier implantation window. Finally, the endometrium can be prepared by

hormone replacement during FET cycles – this is also favored by an increasing number of clinicians as it is simple to apply, and it reduces both the monitoring frequency and cycle cancellation rate. The corpus luteum does not form endogenously in FET cycles due to the absence of ovulation; therefore, secretory transformation of the endometrium – prior to ET and maintenance of normal embryonic development after ET – is dependent on exogenous progesterone supplementation (15–20).

Progesterone plays an important role in endometrial-embryo synchrony and the maintenance of early pregnancy (21) There are currently three routes of progesterone administration in China: oral, intramuscular and vaginal. Intramuscular progesterone administration is frequently used in the clinic as it is inexpensive and both a high serum level and a stable clinical pregnancy rate can be achieved. However, intramuscular progesterone administration is painful, requires daily injections, and may be inconvenient as commute is required of the participant to and from the hospital. Furthermore, intramuscular administration may lead to inflammation at the site of injection, widely resulting in symptoms such as allergic reactions or local panniculitis, which may progress to abscesses (22). Oral medication is convenient, but bioavailability is low due to hepatic first-pass effect. The vaginal route of progesterone administration is convenient, and it achieves a stable endometrial concentration with low serum levels, which reduces the risks of systemic adverse effects. According to the United States Food and Drug Administration, application of vaginal progesterone gel is the only accepted study intervention option for replacement of progesterone in FET cycles (23,24)

No consensus has yet been reached worldwide as to whether the route or dosage of progesterone administration affects clinical outcomes of FET cycles. Chinese clinicians prefer to give a dose of progesterone that is higher than physiological needs for luteal phase support in all protocols. Currently, oral progesterone combined with vaginal progesterone is the preferred regimen for luteal phase support in FET cycles in China. Wang Y et al. reported that the clinical pregnancy rate of combined medication in FET-AC cycle was 40% in a Chinese population(1). In addition, a few Chinese retrospective studies supported the daily use of 90 mg of Crinone® during FET cycles (2–6). The Chinese consensus also supports the use of Crinone® with 20 mg of Duphaston® for FET luteal support (25).This prompts the question as to whether the small dose of oral progesterone is needed. A well-designed randomized and controlled trial is yet to be conducted to compare the clinical outcomes of FET cycles when administering Crinone® on its own versus combination administration. Therefore, in this pilot study, Crinone® on its own will be compared with combination medication (Crinone® plus Duphaston®) for luteal phase support in FET cycles by assessing their effects on the ongoing pregnancy rate. This study will provide preliminary evidence that differentiates the two protocols.

2.3 Benefit/Risk Assessment

Crinone® and Duphaston® are both currently on the market and have already been evidenced to be well tolerated.

3 Objectives and Endpoints

Objectives	Endpoints (Outcome Measures)
Primary	
To investigate the ongoing pregnancy rate of Crinone® compared to Crinone® in combination with Duphaston® during artificial FET cycles in Chinese population.	Ongoing pregnancy (at 10-12 weeks of pregnancy [8-10 weeks after ET]). See Section 9.4.1.1 for the statistical aspects of the endpoints.
Secondary	
To evaluate the efficacy of Crinone® compared to Crinone® in combination with Duphaston® for luteal phase support in artificial FET cycles.	• β-hCG positive • Implantation • Clinical pregnancy See Section 9.4.1.2 for the statistical aspects of the endpoints.
To evaluate the safety of Crinone® compared to Crinone® in combination with Duphaston® for luteal phase support in artificial FET cycles.	• Early abortion • Bleeding (luteal phase, vaginal) • The safety profile of the study intervention will be assessed according to Section 8.2. See Section 9.4.1.2 for the statistical aspects of the endpoints.

4 Study Design

4.1 Overall Design

This is a Phase IV, local, single center, open label, pilot, randomized controlled clinical study to compare the efficacy and safety of Crinone® versus combination medication. The study population are infertile women who receive FET in ACs This study plans on including 334 participants from a single reproductive center over 25 months. Participants that enter the study will be randomized into either of the two groups. The study intervention drug received by the participant is determined based on the result of randomization. The randomization procedure is described in Section 6.3. The overall scheme of the study is in Section 1.2 and the Schedule of Activities at each visit can be found in Section 1.3.

The participants will sign an ICF; the participants are free to withdraw at any time without prejudice to their medical care, and they are not obliged to state their reasons for withdrawal. Upon site initiation, the Investigator site will enroll the eligible participants who meet the inclusion and none of the exclusion criteria in a consecutive manner until the enrollment target is reached. The study will consist of a screening period, followed closely by procedures from endometrial transformation to ongoing pregnancy assessment, which lasts for approximately 75 days. Study treatment will start from the day of endometrial transformation (Day -5) until ongoing pregnancy assessment, which occurs between 10-12 weeks of pregnancy (8-10 weeks after ET). The middle number of 9 weeks (Day 63) after ET is used to define the study day with a window of 10 days on each side as leeway. The treatment will be administered for approximately 75 days.

Relevant data according to study requirements will be recorded in standard CRF. When the study starts, this reproductive center will include participants who enter the cycle. The information of the qualified yet excluded participants who have signed ICFs will be recorded, and the reason for their exclusion will also be recorded in the CRF. If a participant has entered the study and later discontinue their study intervention, the reason for discontinuing the study intervention will be recorded in the CRF.

Participant follow-up will occur until her ongoing pregnancy is confirmed and/or until End of Study (defined in Section 4.4).

4.2 Scientific Rationale for Study Design

CCI [redacted]

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4.3 Justification for Dose

Currently, oral progesterone combined with vaginal progesterone is the preferred regimen for luteal phase support in FET cycles in China. Wang Y et al. reported that the clinical pregnancy rate of combined medication (90 mg of Crinone® combined with 20 mg of Duphaston®) in FET-AC cycle was 40% in a Chinese population (1). In addition, a few Chinese retrospective studies supported the daily use of 90 mg of Crinone® during FET cycles (2–6).

4.4 End of Study Definition

A participant has completed the study if she has completed all study parts, including the last visit or the last scheduled procedure shown in Section 1.3 (Schedule of Activities).

The end of the study is defined as the date of the last visit of the last participant or the last scheduled procedure shown in Section 1.3 (Schedule of Activities) for the last participant in the study.

The date and the reason for the completion / withdrawal from the study intervention or study (see Section 7) will be collected.

5 Study Population

The criteria in Sections 5.1 (Inclusion Criteria) and 5.2 (Exclusion Criteria) are designed to enroll only participants, who are appropriate for the study; thereby, ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a participant is suitable for this study.

Prospective approval of protocol deviations to inclusion and exclusion criteria, also known as protocol waivers or exemptions, are not permitted.

Before performing any study assessments that are not part of the participant's routine medical care, the Investigator will confirm that the participant or the participant's legal representative has provided written informed consent, as indicated in Appendix 2 (Study Governance).

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

1. Are 20 through 38 years old women who will receive artificial FET cycle study interventions
2. No more than two Day 5 embryos are planned to be transferred (follow the clinical practice of the study site)
3. Have received estradiol valerate for no more than 20 days
4. Have a transitional-endometrium of ≥ 8 mm
5. Have normal uterine cavity
6. Can give signed informed consent, as indicated in Appendix 2 (Study Governance), which includes compliance with the requirements and restrictions listed in the ICF and this protocol.
7. Are willing to follow the study protocol and able to complete the study

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. ≥3 previously failed cycles of ET
2. Participants with diseases that cannot tolerate pregnancy
3. Hydrosalpinx
4. Severe endometriosis (Endometriosis American Society for Reproductive Medicine (ASRM) criteria from 1996)

5. Known hypersensitivity to progesterone, the excipients of Crinone® and Duphaston®
6. Vaginal bleeding of unknown origin
7. History of recurrent miscarriages
8. Vaginitis
9. Thromboembolic diseases (thrombophlebitis, thromboembolic disorder, or cerebral apoplexy) or patients with an history of these conditions
10. Known or suspected progestogen-dependent neoplasm
11. Participation in another clinical trial within the past 30 days
12. Contraindications of both Crinone® and Duphaston®
13. Participants with potential risk (The participants/parterner are from high risk region which can be tracked by health barcode) or symptoms of COVID-19 (eg. fever, cough etc).

5.3 Lifestyle Considerations

Not applicable

5.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6 Study Interventions

Study intervention is any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant per the study protocol.

6.1 Study Interventions Administration

Study Intervention Name:	Crinone®	Duphaston®
Dose Formulation:	Progesterone gel 8% (90 mg)	Tablet
Unit Dose Strength(s)/Dosage Level(s):	90 mg	10 mg/tablet
Route of Administration:	Intravaginal	Oral
Dosing Instructions:	1 gel, q.d. in the morning	1 tablet, b.i.d
Supplier/Manufacturer:	Merck will provide Crinone® for free	Prescribed for participants in the clinic by Investigators
Packaging and Labeling	• every box contains 15 applicators • The validity period is 36 months • Each applicator will be packaged and labeled per all applicable regulatory requirements and Good Manufacturing Practice Guidelines.	• According to the package labelling as prescribed by the Investigator

6.2 Study Interventions Preparation, Handling, Storage, and Accountability

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

- Upon receipt of the study intervention(s), the Investigator or designee must confirm appropriate temperature conditions have been maintained during transit and any discrepancies are reported and resolved before use. Also, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate document and returning it to the location specified. A copy will be archived for the Investigator Site File.

- Only participants enrolled in the study may receive study intervention(s) and only authorized site staff may supply it. All study intervention(s) must be stored in a secure, environmentally-controlled, and monitored (manual or automated) area, in accordance with the labeled storage conditions, and with access limited to the Investigator and authorized site staff.
- Dispensing will be recorded on the appropriate accountability forms so that accurate records will be available for verification at each monitoring visit.
- Study intervention(s) accountability records at the study site will include the following:
  - Confirmation of receipt, in good condition and in the defined temperature range.
  - The inventory provided for the clinical study and prepared at the site.
  - The dose(s) each participant used during the study.
  - The disposition (including return, if applicable) of any unused study intervention(s).
  - Dates, quantities, batch numbers, expiry dates, and the participant numbers.
- The Investigator site will maintain records, which adequately documents that participants were provided the doses specified in this protocol, and all study intervention(s) provided were fully reconciled.
- Unused study intervention(s) must not be discarded or used for any purpose other than the present study. No study intervention that is dispensed to a participant may be re-dispensed to a different participant.
- A Study Monitor will periodically collect the study intervention(s) accountability forms.
- Further guidance and information for the final disposition of unused study intervention(s) are provided in the Study Reference Manual.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

Participants will be randomized in a 1:1 ratio to receive either Crinone® or the combination medication group on the day of ET.

The trial is designed as a single center trial, and randomization will be conducted on the ET day by using the block permutation method and stratified by age group (ages 20 to 35 years, or ages 35 years and over), which will guarantee that a balanced number of participants will be obtained between Crinone® and the combination medication groups inside each age stratum. If an error occurs (for example if the wrong list is used), the participant should continue with their assigned study intervention, and the next participant should still be assigned the next available number and study intervention of the correct list. The site must not attempt to "correct" for the error (i.e., if a participant is on the Crinone® list instead of the

combination medication group list, the site must not try to assign the Crinone® participant to the combination medication group list to offset this). Since ACCESS is an open-labeled observational study, baseline characteristic analysis will be presented to show whether the participants were well-stratified by age between the two study intervention groups.

6.3.2 Blinding

Not applicable

6.4 Study Intervention Compliance

See Section 6.2 for dispensing and accountability of the study interventions.

Crinone® will be provided for free and Duphaston® will be prescribed by the physicians and will be bought by the participants themselves. Study intervention administration must be recorded in the CRF as applicable.

The acceptable compliance for this study is at a minimum of 80%.

6.5 Concomitant Therapy

Record in the CRF all concomitant therapies (e.g., medicines or nondrug interventions) used from the time the participant signs the informed consent until completion of the study, including any changes. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name, reason for use, dates administered, and dosing information.

Contact the Medical Monitor for any questions on concomitant or prior therapy.

6.5.1 Rescue Medicine

Rescue medications may be administered to address ineffective study intervention, anticipated adverse reactions or anticipated emergency situations.

Rescue medicine will be defined as the drug changed or dosage changed when the patient experiences threatened abortion. Rescue medicines will not be considered as prohibited medicines. Participants who use rescue medicines will be allowed to remain in the study.

6.5.2 Permitted Medicines

Medications that are considered necessary to protect the participant's welfare and will not interfere with the trial medication may be given at the Investigator's discretion.

Any medicines that are considered necessary to protect the participant's welfare in emergencies may be given at the Investigator's discretion, regardless if it results in a protocol deviation.

6.5.3 Prohibited Medicines

Other types of progesterone used one month before and during this study such as Utrogestan, intramuscular injections of progesterone; other ongoing vaginal medications. If any prohibited medicines are used, study participants will be allowed to remain on study provided that the Sponsor and the Investigator agrees. Rescue medicines are not considered prohibited medicines.

6.5.4 Other Interventions

Estradiol valerate will be administered according to local practice.

All participants will receive oral estradiol valerate continuously and the dose of estradiol valerate will be adjusted according to local practices.

6.6 Dose Selection and Modification

Not applicable.

6.7 Study Intervention after the End of the Study

The Sponsor will not provide any additional care to participants after they leave the study.

6.8 Special Precautions

Not applicable.

6.9 Management of Adverse Events of Interest

Refer to the package inserts for possible adverse drug reactions to Crinone® and Duphaston®. The management of adverse drug reactions should be based on the Investigator's judgment according to the medical condition of the participant.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

See Section 7.2.

7.2 Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study intervention and the study if any one or more of the below criteria are met:

- Adverse event (AE)/SAE, according to the discretion of the Investigator
- Participant is lost to follow up
- Withdraw consent
  Participants will be informed that they have the right to withdraw from the trial at any time without prejudice to their medical care, and that they are not obligated to state their reasons for withdrawal. Participant data will be included in the analyses up until consent is withdrawn.

The trial exit electronic CRF will be completed when a participant is withdrawn from the trial. All withdrawals must be fully documented in the source documents.

A participant is considered having completed the observation period (i.e., not withdrawn from study intervention or study) when

- The participant achieves ongoing pregnancy

  Or

- FET cycle may be considered finished when any one of the following applies:
  - β-hCG is negative (on the 13-15th day after ET）
  - Clinical pregnancy is negative (between the 4-6th week post-transfer）
  - Fetal heart beat stops before 10-12 weeks of pregnancy (8-10 weeks after ET).

7.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain if the participant wants to or should continue in the study.

- Before a participant is deemed "lost to follow-up", the Investigator or designee must make every effort to regain contact with the participant: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the participant's last known mailing address, and 3) if a participant has given the appropriate consent, contact the participant's general practitioner for information. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, she will be considered to have withdrawn from the study.

8 Study Assessments and Procedures

The visit procedures are described in the Schedule of Activities (Section 1.3) and Appendix 4.

8.1 Efficacy Assessments

8.1.1 Primary endpoints

Ongoing pregnancy (at 10-12 weeks of pregnancy [8-10 weeks after ET]). Ongoing pregnancy is defined in Section 9.4.1.1.

8.1.2 Secondary endpoints:

- β-hCG positive
- Implantation
- Clinical pregnancy
- Early abortion
- Bleeding (luteal phase, vaginal)
- The safety profile of the study intervention will be assessed according to Section 8.2.

The definitions are provided in Section 9.4.1.2.

8.2 Safety Assessments and Procedures

The safety profile of the study intervention will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs, physical examination findings and laboratory tests.

Comprehensive assessment of any potential toxicity experienced by each participant will be conducted starting when the participants give informed consent and throughout the study. The Investigator will report any AEs, whether observed by the Investigator or reported by the participant; the reporting period is specified in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information).

8.2.1 Physical Examinations

- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE and a SAE are in Appendix 3.

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

The AE reporting period for safety surveillance begins upon endometrial transformation (Visit 2) and continues until the End of Study Visit.

Any SAE assessed as related to study intervention must be recorded and reported, as indicated in Appendix 3, whenever it occurs, irrespective of the time elapsed since the last administration of study intervention.

The method of recording, evaluating, and assessing causality of AEs (including SAEs) and the procedures for completing and transmitting SAE reports are in Appendix 3.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

At each study visit, the participant will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the participant's condition will be recorded as AEs, regardless if reported by the participant or observed by the Investigator.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the CRF. All SAEs must be additionally documented and reported using the appropriate Report Form as specified in Appendix 3.

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

AEs are recorded and assessed continuously throughout the study, as specified in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information) and are assessed for their outcome at the End of Study Visit. All SAEs ongoing at the End of Study Visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the participant is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. Further information on follow-up procedures is given in Appendix 3 (Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reports).

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving study participants to the Independent Ethics Committee (IEC)/ Institutional Review Board (IRB) that approved the study.

In accordance with International Council for Harmonization (ICH) Good Clinical Practice (GCP), the Sponsor/designee will inform the Investigator of findings that could adversely affect the safety of participants, impact the conduct of the study or alter the IEC's/IRB's approval/favorable opinion to continue the study. In line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations regarding Safety Report notifications to Investigators will be considered.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

For studies covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidance documents.

8.3.5 Pregnancy

Not applicable since ongoing pregnancy is the primary endpoint of the study.

8.4 Study intervention Overdose

For this study, any dose of Crinone® greater than 90 mg/p.v./q.d in the single treatment group, or Crinone® at 90 mg/p.v./q.d and Duphaston® at 10 mg/p.o./b.i.d in the combination treatment group will be considered an overdose. The schedule can be seen in Section 1.3. In case of an overdose, the participant will be assessed by Investigators as to whether they will continue participating in the study or not. Rescue medicines that are administered are not considered overdosing.

Even if it not associated with an AE or a SAE, any overdose is recorded in the CRF and reported to drug safety in an expedited manner. Overdoses are reported on a SAE Report Form, following the procedure in Appendix 3, section on Reporting Serious Adverse Events.

8.5 Pharmacokinetics

Not applicable.

8.6 Pharmacodynamics

Not applicable.

8.7 Pharmacogenetics

Not applicable.

8.8 Biomarkers

Not applicable.

8.9 Immunogenicity Assessments

Not applicable

9 Statistical Considerations

9.1 Statistical Hypotheses

For this open label, exploratory, randomized, control, pilot trial, there will be no confirmative hypothesis testing considered.

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[redacted]

9.3 Populations for Analyses

The analysis populations are specified below. The final decision to exclude participants from any analysis population will be made during a data review meeting prior to database lock.

Analysis Set	Description
Intention-to-Treat (ITT)	The ITT Population will include all participants who receive at least one dose of randomized study intervention. Participants will be analyzed according to the study intervention they were initially assigned.
Per-Protocol (PP)	Includes all participants in ITT population without any major protocol violations.
Safety Population	Include all participants who have received at least one dose of study intervention. Participants will be analyzed according to the actual study intervention they received

9.4 Statistical Analyses

9.4.1 Endpoints

9.4.1.1 Primary Endpoints

- Ongoing pregnancy (at 10-12 weeks of pregnancy (8-10 weeks after ET))

  Definition: The presence of viable intra uterine fetus detected by ultrasound examination in 12 weeks of pregnancy.

9.4.1.2 Secondary Endpoints

- β-hCG positive

  Definition: A pregnancy diagnosed by the detection of β-hCG in serum

- Implantation:

  Definition: The number of gestational sacs observed by ultrasound scan

- Clinical pregnancy

  Definition: A pregnancy diagnosed by ultrasound of one or more gestational sacs or definitive clinical signs of pregnancy. It includes ectopic pregnancy. Note: Multiple gestational sacs are counted as one clinical pregnancy.

- Early abortion

  Definition: The spontaneous loss of an intra-uterine pregnancy prior to 12 completed weeks of gestational age.

- Bleeding (luteal phase, vaginal)

  Definition: The bleeding data will be collected in a CRF after each visit by Investigators according to original medical documents.

  - Luteal phase bleeding: defined as the onset of any bleeding after ET and prior to the pregnancy test. The luteal phase bleeding rate will be assessed in each group and analysed according to the pregnancy outcomes.
  - Vaginal bleeding is defined as any bleeding recorded in the CRF after a pregnancy test via serum β-hCG and is considered as an AE. The vaginal bleeding rate will be assessed and compared in both groups at each visit.

9.4.1.3 Safety Endpoint(s)

Safety parameters will include the incidence and severity of all AEs.

9.4.2 General Considerations

Descriptive Statistics

For the continuous parameters, the following statistics will be presented: Number (N) of participants, mean, standard deviation (SD), median, first quartile (q1), third quartile (q3), minimum, and maximum. The number of participants with missing values ('Missing') will be presented based on observed case data if necessary. An overall column will also be added where appropriate.

For categorical parameters, the total number ('N') of participants and percentages will be presented. The number of participants with missing values ('Missing') will be presented based on observed case data if necessary. An overall column will also be added where appropriate.

Method for handling missing data

Normally, missing data will not be imputed. If the participant does not have the required evidence for ovulation, follicular development, or pregnancy, then the participant will be counted as a failure for that particular endpoint.

Should a specific endpoint need another method to handle missing data, this will be specified in the Statistical Analysis Plan.

9.4.3 Analysis of Endpoints

Endpoint	Statistical Analysis Methods
Primary	The analysis of the primary endpoint in this pilot study is essential for further planning of formal clinical trials. The analysis for the primary endpoint will estimate the ongoing pregnancy rate and its corresponding 95% CI for each group, and difference in ongoing pregnancy rate between combination medication and Crinone® and its corresponding 90% CI. The CIs for each treatment group will be calculated with the Clopper-Pearson method. The CI for the difference between the two treatment groups will be calculated with the Pearson chi-square test **Ongoing pregnancy rate**: the number of ongoing pregnancies expressed per 100 ET cycles (from the start date of first ET to the End of Study). Since the number of embryos transferred is medically known to have an impact on the chance of achieving an ongoing pregnancy rate, the rate of participants with only 1 embryo transferred within each arm will be examined. If the data suggest a possible imbalance between the two arms, pertinent subgroup analyses of the primary endpoint in participants with only 1 embryo transferred and in participants with 2 embryos transferred may be performed. Details will be specified in the Statistical Analysis Plan.
Secondary	The analyses of secondary endpoints will take the similar manner as primary endpoint. Implantation rate: The number of gestational sacs observed divided by the number of embryos transferred (usually expressed as a percentage, %). β-hCG positive rate: the number of β-hCG positive participants expressed per 100 ET cycles. Clinical pregnancy rate: the number of clinical pregnancies expressed per 100 ET cycles.

Endpoint	Statistical Analysis Methods
	Luteal phase bleeding rate：the number of the participants with luteal phase bleeding expressed per 100 embryos transferred cycles. Vaginal bleeding rate: the number of the participants with vaginal bleeding expressed per 100 embryos transferred cycles.

9.4.4 Safety Analyses

Safety Analyses will be performed using the Safety population.

Data on AEs will be collected on scheduled and unscheduled visits, based on information spontaneously provided by the participant and/or by questioning the participant. The most current version of Medical Dictionary for Regulatory Activities (MedDRA) and the World Health Organization Drug Dictionary (WHODRUG) coding dictionaries will be used for AEs, medical conditions, and concomitant medications. Number and percentage of patients with AEs or SAEs will be presented according to System Organ Class and the preferred term from the MedDRA dictionary.

9.4.5 Sequence of Analyses

No formal interim analyses are planned.

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11 Appendices

Appendix 1 Abbreviations

AC	Artificial cycle
AE	Adverse event
ALT	Alanine aminotransferase
ART	Assisted reproductive treatment
ASRM	American Society for Reproductive Medicine
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case report form
CT	Computed tomography
ECG	Electrocardiogram
EDC	Electronic data capture
ET	Embryo transfer
FET	Frozen-thawed embryo transfer
GCP	Good clinical practice
β-hCG	Beta human chorionic gonadotrophin
HIPAA	Health Insurance Portability and Accountability Act
I/E	Inclusion/Exclusion
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent ethics committee
IRB	Institutional review board
ITT	Intention-to-treat
IVF	In vitro fertilization
MRI	Magnetic resonance imaging
PP	Per protocol
SAE	Serious adverse event
SUSAR	Suspected unexpected serious adverse reactions
MedDRA	Medical Dictionary for Regulatory Activities
WHODRUG	World Health Organization Drug Dictionary

Appendix 2 Study Governance

Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information, as requested, for the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. This information is required during the study and for 1 year after completion of the study.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions on the study.
- Participants must be informed that their participation is voluntary.
- Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; local regulations; ICH guidelines; Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable; and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- If the ICF is updated during their participation in the study, participants must be re-consented to the most current, approved version.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- The original signed and dated consent will remain at the Investigator's site and must be safely archived so that it can be retrieved at any time for monitoring, auditing and inspection purposes.

Data Protection

- The Sponsor will assign a unique identifier to participants after obtaining their informed consent. All participant records or datasets transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred.
- The Sponsor must inform participants that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain participants' confidentiality.

Study Administrative

The Principal Investigator listed on the title page represents all Investigators for decisions and discussions on this study, per ICH GCP. The Coordinating Investigator will provide expert medical input and advice on the study design and execution and is responsible for the review and signoff of the clinical study report.

The study will appear in the following clinical studies registries: clinicaltrials.gov

Details of structures and associated procedures will be defined in a separate Study Reference Manual.

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations

The Investigator must submit the protocol, protocol amendments (if applicable), ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) to an IRB/IEC and the IRB/IEC must review and approve them before the study is initiated.

Any protocol amendments (i.e., changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants. When applicable, amendments will be submitted to the appropriate Health Authorities.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently per the IRB's/IEC's requirements, policies, and procedures.
- Notifying the IRB/IEC of SAEs or other significant safety findings, as required by IRB/IEC procedures
- Providing oversight of the study conduct at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

Emergency Medical Support

- The Sponsor or designee will provide Emergency Medical Support cards to participants for use during the study. These provide the means for participants to identify themselves as participating in a clinical study. Also, these give health care providers access to any information about this participation that may be needed to determine the course of medical

study intervention for the participant. The information on the Emergency Medical Support card may include the process for emergency unblinding (if applicable).

- The first point of contact for all emergencies will be the clinical study Investigator caring for the participant. Consequently, the Investigator agrees to provide his or her emergency contact information on the card. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard process established for Investigators.

Clinical Study Insurance and Compensation to Participants

Insurance coverage will be provided for each country participating in the study. Insurance conditions shall meet good local standards, as applicable.

Clinical Study Report

After study completion, the Sponsor will write a clinical study report in consultation with the Principal Investigator.

Publication

- The first publication will include the results of the analysis of the primary endpoints and will include data that provided evaluable data. The Investigator will inform the Sponsor in advance about any plans to publish or present data from the trial. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require review by the Sponsor before submission. The Sponsor will not suppress publication, but maintains the right to delay publication in order to protect intellectual property rights.
- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows Merck to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by agreement.
- Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

After completion of the trial, a clinical trial report will be written by the Sponsor in conjunction with the Principal Investigator following the guidance in ICH Topic E3. The report must fully present the study objectives, methods, results, limitations of the study, and the interpretation of the findings.

Data Quality Assurance

- All participant study data will be recorded on printed or electronic CRFs or transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the CRF. Details for managing CRFs are in the Study Reference Manual.
- The Investigator must maintain accurate documentation (source data) that supports the information in the CRF.
- The Investigator must permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are in the Monitoring Plan.
- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. PDF files of the CRFs will be provided to the Investigators at study completion.
- Study monitors will perform ongoing source data verification to confirm that data in the CRF are accurate, complete, and verifiable; that the safety and rights of participants are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.
- The Investigator must keep a paper or electronic file (medical file and original medical records) at the site for each study participant. The file must identify each participant, contain the following demographic and medical information for the participant, and should be as complete as possible:
    - Participant's full name, date of birth, sex, height, and weight
    - Medical history and concomitant diseases

- Prior and concomitant therapies (including changes during the study)
- Study identifier (i.e., the Sponsor's study number) and participant's study number.
- Dates of entry into the study (i.e., signature date on the informed consent) and each visit to the site
- Any medical examinations and clinical findings predefined in the protocol
- All AEs
- Date that the participant left the study, including any reason for early withdrawal from the study or study intervention, if applicable.

- All source data must be filed (e.g., computed tomography [CT] or magnetic resonance imaging [MRI] scan images, electrocardiogram [ECG] recordings, and laboratory results). Each document must have the participant number and the procedure date; ideally, printed by the instrument used for the procedure. As necessary, medical evaluation of these records should be performed, documented, signed and dated by the Investigator.
- Data recorded on printed or electronic CRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The study monitors will use printouts of electronic files for source data verification. These printouts must be signed and dated by the Investigator and kept in the study file.
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator ensures that no destruction of medical records is performed without the Sponsor's written approval.
- Definition of what constitutes source data is found in the source document agreement.

Study and Site Closure

- The Sponsor reserves the right to close the study site or terminate the study at any time and for any reason. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been completed.
- The Investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
- Reasons for the early closure of a study site by the Sponsor or Investigator may include:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
  - Inadequate recruitment of participants by the Investigator
  - Discontinuation of further development of the Sponsor's compound

Appendix 3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions

Adverse Event

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product, regardless of causal relationship with this study intervention. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, regardless if it is considered related to the medicinal product.

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

The Investigator is required to grade the severity or toxicity of each AE.

Investigators must assess the severity of AEs per the Qualitative Toxicity Scale, as follows:

Mild: The participant is aware of the event or symptom, but the event or symptom is easily tolerated.

Moderate: The participant experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.

Severe: Significant impairment of functioning: the participant is unable to carry out his or her usual activities.

Investigators must also systematically assess the causal relationship of AEs to study intervention (including any other non-study interventions, radiation therapy, etc.) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the study intervention include, but may not be limited to, temporal relationship between the AE and the study intervention, known side effects of study intervention, medical history, concomitant medication, course of the underlying disease, and study procedures.

Unrelated: Not reasonably related to the study intervention. AE could not medically (pharmacologically/clinically) be attributed to the study intervention under study in this clinical study protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the study intervention. AE could medically (pharmacologically/clinically) be attributed to the study intervention under study in this clinical study protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (e.g., on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to study intervention discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (e.g., anemia or increased alanine aminotransferase [ALT]) must be reported as the AE rather than the abnormal value itself.

Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening. Life-threatening refers to an event in which the participant is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongs an existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is otherwise considered to be medically important. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive study intervention in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

  In this clinical study, any spontaneous abortion, ectopic pregnancy, should be considered as an SAE.

  For the purposes of reporting, any suspected transmission of an infectious agent via a study intervention is also considered an SAE.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study intervention or procedures (e.g., an overnight stay to facilitate intravenous therapy) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (i.e., undesirable effects of any administered study intervention) must be documented and reported as SAEs.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial study visit that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions, and are not to be considered AEs.

Recording and Follow-Up of AE and/or SAE

It is important that each AE report include a description of the event, its duration (onset and resolution dates and also onset and resolution times, when it is important to assess the time of AE onset relative to the recorded study intervention administration time), its severity, its causal relationship with the study intervention, any other potential causal factors, any study intervention given or other action taken, including dose modification or discontinuation of the study intervention, and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented.

Specific guidance is in the CRF Completion and Monitoring Conventions provided by the Sponsor.

Reporting Serious Adverse Events

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 HOURS after becoming aware of the event) inform the Sponsor or its designee using the paper report form. Names, addresses, and telephone and fax numbers will be included on the paper form.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, a paper SAE report form must be completed immediately thereafter.

Relevant informstion may be provided in parallel (e.g., medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (e.g., laboratory results, hospital report, autopsy report).

The Investigator must respond to any request for follow-up information (e.g., additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the study monitor, although in exceptional circumstances the drug safety department may contact the Investigator directly to obtain further information or to discuss the event.

Appendix 4 Visit Procedures

All participants' data will be collected in anonymity. The participants are assigned to the two study intervention groups at the ratio of 1:1 using a permuted block randomization according to a randomization schedule generated by the statistician using a computer program. Each participant will have a unique participant number assigned to her and this will be referenced throughout the study as the participant's identifier. The Investigator should keep a separate code identification list with all the participants' information to be retained at the site. Details of randomization are in Section 6.3.

After randomization, the participants will receive either Crinone® or Crinone® in combination with Duphaston® for luteal phase support in FET AC.

The data collection time points for the two protocols are as follows:

1. Screening/Baseline
2. Endometrial transformation day
3. ET day
4. β-hCG test: Serum β-hCG test 13 to 15 days after ET
5. Clinical Pregnancy Assessment: Ultrasound examination 4 to 6 weeks after ET
6. Ongoing Pregnancy Assessment (presence of viable fetus at 10-12 weeks of pregnancy [8-10 weeks after ET])

All procedures described in Appendix 4 will be conducted according to the routine practices of the study site.

Visit 1 (baseline evaluation):

The participant will be informed of the study objectives and overall requirements at the initial study visit and written informed consent will be obtained prior to any study-specific assessments. Participants may have already initiated estradiol valerate use. The participant will then undergo a brief clinical evaluation to ensure compliance with the inclusion and exclusion criteria to determine eligibility (see Section 5).

Data for all participants will come from the participants' screening or baseline visits and the participants' medical records.

The following must be completed at Visit 1:

- Visit date
- Participant name will be recorded and kept confidentially in the clinic solely for the purposes of generating a unique participant number, which will be used to identify each participant in the study anonymously.

- Demographics include age, gender and date of birth
- Physical exam and vital signs
- Weight and height
- Clinical and gynecological examination (pelvic examination will be performed); examinations from medical history prior to signing the ICF is also accepted per the Investigator's decision
- Gynecological history: duration of infertility, menstrual cycle, history of miscarriages, history of pelvic surgery, history of ovarian surgery.
- Medical history and concomitant illness
- Any concomitant medication taken by the participant when entering the study
- Concomitant medications prescribed and reasons
- Ultrasound without abnormal findings (endometrium thickness will be measured); examinations from medical history prior to the initiation of estradiol valerate before signing the ICF is also accepted per the Investigators decision
- Serum β-hCG levels must be negative; examinations from medical history prior to signing the ICF is also accepted per the Investigators decision
- Check I/E criteria
- Date of initiation of estradiol valerate (if applicable)
- Initial dose of estradiol valerate (if applicable)
- Details of dose adjustments of estradiol valerate if any (if applicable)
- Duration and total dosage of estradiol valerate (if applicable)

Visit 2 (endometrial transformation day)

The participants should come to the clinic to measure their endometrial thickness on endometrial transformation day. Should the endometrial thickness be ≥8 mm, Crinone® will be administered at a dose of 90 mg/d for 4-6 days to assist the secretory transformation of the endometrium. The following data will be collected:

- Date of initiation of estradiol valerate
- Initial dose of estradiol valerate
- Details of dose adjustments of estradiol valerate if any
- Duration and total dosage of estradiol valerate
- Date of initiation of Crinone®

- Endometrial thickness before initiation of Crinone® (Endometrial thickness will be measured by ultrasound. However, if the ultrasound was performed on the endometrial transformation day prior to signing the ICF, a new ultrasound is not required.)
- Check I/E criteria
- Recording of AEs
- Concomitant medications prescribed and reasons.

The total duration of estradiol valerate before the endometrial transformation should be no more than 20 days.

Visit 3 (embryo transfer day)

After 4-6 days of assisted secretory transformation of the endometrium, no more than two D5 embryos will be transferred on the fifth, sixth, or seventh day. After randomization, the luteal phase support study intervention will be initiated.

- Study intervention A (Crinone® group): Randomized participants will be given Progesterone gel 8% (Crinone®) 90 mg/p.v./q.d from the day of endometrial transformation. It will be suggested that they administer the drug in the morning and at the same time of day throughout the trial. A β-hCG test will be done 14 days after ET. If serum β-hCG levels are negative, the study will be discontinued. If the result of the β-hCG test is positive, Crinone® administration will continue with the above regimen. At 35 days after ET, an ultrasound will be done to detect the number of gestational sacs to confirm the results of clinical pregnancy. If clinical pregnancy is positive, continue Crinone® administration until ongoing pregnancy assessment. Should a miscarriage occur at any point, Crinone® administration will be discontinued.

- Study intervention B (Crinone® + Duphaston® group): Randomized participants will be given Progesterone gel 8% (Crinone®) 90 mg/p.v./q.d from the day of endometrial transformation, following which Duphaston® at 10 mg/p.o./bid will be administered from the day of ET. It will be suggested that they administer the drugs in the morning and at the same time of day throughout the trial. A β-hCG test will be done 14 days after ET. If serum β-hCG levels are negative, the study will be discontinued. If the result of the β-hCG test is positive, the combination medication will continue with the above regimen. At 35 days after ET, an ultrasound will be done to detect the number of gestational sacs to confirm the results of clinical pregnancy. If clinical pregnancy is positive, continue combination medication until ongoing pregnancy assessment. Should a miscarriage occur at any point, combination medication will be discontinued.

All participants will receive oral estradiol valerate continuously and the dose of estradiol valerate will be adjusted according to local practices.

The following data will be collected:

- Duration and total dosage of estradiol valerate

- Date of ET
- Number of embryo(s) transferred (no more than 2)
- Embryo quality
- Check I/E criteria
- Recording of AEs
- Concomitant medications prescribed and reasons.

Visit 4 (β-hCG positive assessment)

Participants treated by ART are routinely monitored for early detection of pregnancy by measuring serum β-hCG concentration according to the site's routine clinical practices.

After about 13 to 15 days of ET, early detection of pregnancy will be done by measuring β-β-hCG levels using blood tests and the results will be recorded.

The following data will be collected:

- Date of pregnancy assessment
- β-hCG test results (positive or negative)
- Details of luteal phase bleeding, if any
- Recording of AEs
- Concomitant medications prescribed and reasons.

If the result of the pregnancy assessment is negative, procedures related to End of Study visit will be performed.

Visit 5 (Clinical Pregnancy Assessment)

If the result of the β-hCG pregnancy assessment is positive, it will be further confirmed by a clinical pregnancy assessment (by means of an ultrasound examination) 4 to 6 weeks after ET.

The following data will be collected:

- Date of pregnancy assessment
- Pregnancy status
- Positive pregnancy status has to be confirmed by ultrasound examination (presence or non-presence of gestational sac(s), gestational sacs with or without heartbeat, gestational stage at which ultrasound is performed is to be recorded and ectopic pregnancy).
- Details of vaginal bleeding, if any
- Recording of all AEs, expedited reporting of all SAEs

- Concomitant medications prescribed and reasons.

If the result of the pregnancy assessment is negative, procedures related to End of Study visit will be performed.

Visit 6 (Ongoing Pregnancy assessment)

Ongoing pregnancy is defined as the presence of viable intra uterine fetus detected by ultrasound examination in 12 weeks of pregnancy. The following data will be collected:

- End of study intervention date
- Singleton pregnancy / multiple pregnancy
- Status of ongoing pregnancy
- Early miscarriage, if any
- Details of vaginal bleeding, if any
- Recording of AEs
- Concomitant medications prescribed and reasons.

If the status of ongoing pregnancy is confirmed negative, all procedures related to End of Study Visit will be performed.

If the status of ongoing pregnancy is negative and if it is due to an abortion - the reason for abortion should be recorded.

End of Study

The date and the reason of the completion/withdraw from study intervention or study (see Section 7.2) will be collected.

Appendix 5 Sponsor Signature Page

Study Title:	Comparison of Crinone® versus combination medication for luteal phase support on the ongoing pregnancy rate of frozen-thawed cycle in Chinese population: a randomized, interventional, open-label, Phase IV, single center, pilot study
Regulatory Agency Identifying Numbers:	NA
Clinical Study Protocol Version:	19Jan2021/ Version 2.0-CHN

I approve the design of the clinical study:

PPD

Signatu

PPD

Date of Signature

Name, academic degree:	PPD
Function/Title:	
Institution:	Merck Serono Co., Ltd., Beijing, China
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Telephone number:	PPD
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E-mail address:	

Appendix 6 Principal Investigator Signature Page

Study Title:	Comparison of Crinone® versus combination medication for luteal phase support on the ongoing pregnancy rate of frozen-thawed cycle in Chinese population: a randomized, interventional, open-label, Phase IV, single center, pilot study
Regulatory Agency Identifying Numbers:	NA
Clinical Study Protocol Version:	19Jan2021/ Version 2.0-CHN
Site Number:	001

I approve the design of the clinical study, am responsible for the conduct of the study at this site, and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council on Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

PPD

Signature

PPD

Date of Signature

Name, academic degree:	PPD
Function/Title:	
Institution:	
Address:	
Telephone number:	
Fax number:	
E-mail address:	