FERRING
PHARMACEUTICALS

Protocol

Title of trial: A Prospective, Multi-Center, Non-Comparative Trial of the Clinical Safety of the Progesterone Vaginal Ring in Women Undergoing Assisted Reproductive Technology (ART) Procedures
Sponsor trial code: 000293
Date: 09 Aug 2019

CLINICAL TRIAL PROTOCOL

A Prospective, Multi-Center, Non-Comparative Trial of the Clinical Safety of the Progesterone Vaginal Ring in Women Undergoing Assisted Reproductive Technology (ART) Procedures

Trial 000293

SARA
Safety Assessment of Progesterone Vaginal Ring in Women Undergoing ART

IND Number:	**070785**
Investigational Medicinal Product:	Progesterone vaginal ring (PVR)
Indication:	Progesterone supplementation in women undergoing ART
Phase:	3b
Name and Address of Sponsor:	Ferring Pharmaceuticals Inc. 100 Interpace Parkway Parsippany, NJ 07054 United States Tel: (+1) 973-796-1600
GCP Statement:	This trial will be performed in compliance with GCP.

SYNOPSIS

TITLE OF TRIAL

A Prospective, Multi-Center, Non-Comparative Trial of the Clinical Safety of the Progesterone Vaginal Ring in Women Undergoing Assisted Reproductive Technology (ART) Procedures

Short title: SARA (Safety Assessment of Progesterone Vaginal Ring in Women Undergoing ART)

SIGNATORY INVESTIGATOR

Laurel Stadtmauer, MD, PhD.
The Jones Institute for Reproductive Medicine, Norfolk, Virginia.

TRIAL SITE(S)

Approximately 15 sites in the United States

PLANNED TRIAL PERIOD		CLINICAL PHASE
First subject first visit:	Q3 2018	3b
Last subject last visit:	Q3 2019	

BACKGROUND AND SCIENTIFIC JUSTIFICATION FOR CONDUCTING THE TRIAL

Successful human reproduction is dependent upon the influence of progesterone on endometrial structure and receptivity. Once the corpus luteum is formed after ovulation, it begins to secrete progesterone, which is necessary and sufficient to decidualize the endometrium to facilitate implantation. If conception and implantation occur, increasing concentrations of human chorionic gonadotropin (hCG) drive continued secretion of progesterone from the corpus luteum, which is critical for the maintenance of the endometrium. Progesterone continues to be produced by the corpus luteum until the seventh or eighth week of gestation, at which time the placenta becomes the primary site of production for the remainder of pregnancy.

Administration of exogenous progesterone to support luteal function has been utilized in the treatment of infertility, particularly with ART. A number of studies have demonstrated that the use of gonadotrophin-releasing hormone analogs during controlled ovarian stimulation is associated with defects in corpus luteal function. Progesterone supplementation after the transfer of a fresh, autologous embryo has been shown to improve pregnancy rates.

Vaginal routes of progesterone administration have been shown to allow effective targeted delivery for various indications, including supplementation of corpus luteal function. The vaginal route offers several important advantages over other methods: it is convenient and acceptable for

many subjects, is not painful, does not require any special equipment, systemic levels are low, and it rarely produces allergic or other adverse reactions.

A flexible, non-degradable progesterone vaginal ring (PVR) has been developed, releasing an average of 11 mg progesterone/day consistently over 7 days. The progesterone (20% w/w) is in a micronized formulation and dispersed evenly throughout the ring.

In a pivotal phase 3 trial (Teva Women's Health, Inc. Study DR-PGN-302) evaluating the efficacy and safety of PVR used for luteal phase support in women undergoing in vitro fertilization (IVF), the primary endpoint was clinical pregnancy rate at 8 and 12 weeks of pregnancy. Once-weekly PVR was statistically non-inferior to the active comparator, daily 8% progesterone vaginal gel, in women 18-34 years of age. Secondary efficacy analyses included evaluations of live birth rate, cycle cancellation rate, rate of spontaneous abortion, rate of biochemical pregnancy, and rate of ectopic pregnancy for each treatment group. These rates were similar between the 2 active treatment groups and consistent with reported background rates. Weekly PVR insertion appeared to be safe and well tolerated. Adverse events (AEs) and serious adverse events (SAEs) were similar for both active treatment groups, and no significant safety trends were noted for PVR. Treatment-related AEs were generally similar between the 2 active treatment groups and consistent with the known safety profile of progesterone. Rates of subject discontinuation due to an AE were similar between the treatment groups. AEs related to vaginal bleeding were similar between the 2 active treatment groups. No subject discontinued because of vaginal bleeding, and no subject was switched to an alternative progesterone product because of a bleeding issue. There were no increased rates of cervical/vaginal abrasions or irritation associated with use of a vaginal ring compared with vaginal gel.

Manufacturing enhancements for the PVR were implemented subsequent to the pivotal phase 3 trial. Therefore, a bioequivalence trial was conducted to compare the PVR manufactured using the new process to the ring manufactured by the legacy process (the phase 3 clinical trial material). The results from the pharmacokinetic trial (DR201-BE-10021) demonstrated that the PVR manufactured with the new process was bioequivalent to the PVR produced from the legacy process. The safety data indicated that both rings were similarly safe and well tolerated by healthy, postmenopausal female subjects who were pretreated with estrogen.

The present trial assesses the safety and tolerability of the PVR manufactured with the new process when used for luteal phase support in women undergoing ART. While the design of the proposed trial is similar to that of the pivotal phase 3 trial for the PVR, changes to the way in which AEs are collected and scored have been implemented as requested by the Agency.

OBJECTIVES

Primary objective

- To estimate the cumulative rate of any spontaneous abortion, including spontaneous clinically recognized pregnancy loss and blighted ovum during the trial (up to Week 12 following oocyte retrieval), in subjects treated with PVR following fresh embryo transfer.

Secondary objectives

- To describe the cumulative rate of spontaneous abortions determined at 6 and 10 weeks post-oocyte retrieval, including spontaneous clinically recognized pregnancy loss and blighted ovum, in all subjects treated with PVR.
- To describe the cumulative rate of biochemical abortions determined at 6 and 10 weeks post-oocyte retrieval in all subjects treated with PVR.
- To describe the rate of ectopic and heterotopic pregnancy in all subjects treated with PVR following oocyte retrieval.
- To describe the safety of PVR through the collection of clinical laboratory tests and vital signs in all subjects treated with PVR.
- To assess the safety and tolerability of PVR in all subjects treated with PVR.
- To determine the positive β-hCG rate of subjects treated with PVR following oocyte retrieval.
- To determine the clinical pregnancy rate of subjects treated with PVR following oocyte retrieval.

ENDPOINTS

Primary endpoint

- Cumulative rate of any spontaneous abortion occurring on or before 12 weeks following oocyte retrieval in all subjects treated with PVR and undergoing fresh embryo transfer. *Note*: spontaneous abortion is defined as two positive β-hCG tests occurring at least two days apart on or after 2 weeks post-oocyte retrieval, but followed by observation of any empty intrauterine gestational sac (blighted ovum), intrauterine gestation without a fetal heart beat, or absence of viable fetuses, as documented by transvaginal ultrasound (TVUS).

Secondary endpoints

- Cumulative rate of spontaneous abortions determined at 6 and 10 weeks post-oocyte retrieval in all subjects treated with PVR.
- Cumulative rate of biochemical abortions determined at 6 and 10 weeks post-oocyte retrieval in all subjects treated with PVR. Biochemical abortion is defined as a positive

β-hCG test at 2 weeks and 2 weeks + 3-4 days post-oocyte retrieval, but followed by no observed gestational sac on a later TVUS, or followed by a negative β-hCG test.

- Rate of ectopic and heterotopic pregnancies in all subjects treated with PVR following oocyte retrieval.
- Rate of abnormal findings in clinical laboratory tests and vital signs for all subjects treated with PVR.
- Frequency, intensity/grade, seriousness, and relatedness of adverse events (AEs) for all subjects treated with PVR.
- Frequency, intensity/grade of vaginal bleeding/spotting, vaginal hemorrhage, pain, vaginal infection, and vaginal irritation for all subjects treated with PVR.
- Frequency, intensity/grade, seriousness, and relatedness of AEs associated with vaginal and cervical abrasions and lesions and with vaginal adhesions for all subjects treated with PVR.
- Frequency and reason for PVR discontinuation.
- Positive β-hCG rate (positive serum β-hCG test) at 2 weeks and 2 weeks + 3-4 days post-oocyte retrieval in all subjects treated with PVR.
- Clinical pregnancy rate (TVUS showing at least 1 intrauterine gestational sac with fetal heart beat) at 6 and 10 weeks post-oocyte retrieval in all subjects treated with PVR.

METHODOLOGY

This is an open-label, single-arm, safety trial of PVR for luteal phase support in women undergoing IVF with fresh oocytes. Women between the ages of 18 and 34 years with tubal, idiopathic, male factor, ovulatory dysfunction, or endometriosis-linked infertility, who agree to be considered for inclusion in the trial, will be invited to be seen at the trial site.

Once informed consent is obtained, eligible subjects will be started on an ovarian down-regulation / suppression protocol utilizing combined oral contraceptives supplied by the site for ≥14 days to ≤21 days (based upon the site standard of care), with leuprolide acetate at a dose of 0.1 mL (500 µg)/day beginning 4 days prior to the last birth control pill and for ≥10 days to ≤20 days; ovarian suppression is to begin in the cycle immediately prior to the ovarian stimulation cycle. After suppression, an ovarian stimulation protocol will begin on the second or third day after the start of menses with a reduction in leuprolide acetate dose to 0.05 mL (250 µg/day) followed by an individually determined ovarian stimulation protocol with highly purified, human menopausal gonadotropin (HP-hMG; MENOPUR) at an initial dose of 225 IU/day for 5 days according to label. Based on clinical monitoring, subsequent dosing should be adjusted according to individual subject response. Dose adjustments should not be made more frequently than once every two days and should not exceed 150 IU per adjustment. The maximum daily dose of MENOPUR should not exceed 450 IU and the minimum daily dose should not be lower than 75 IU. MENOPUR dosing should not continue for >20 days and coasting is not allowed. Subjects will be monitored to determine when to trigger ovulation with

hCG. A TVUS will be performed to assess follicle size and serum estradiol levels will be determined. A subject must have at least 2 follicles ≥17 mm (mean of 2 dimensions) to receive the hCG trigger. Subjects who do not reach this threshold after 20 days of stimulation are to be discontinued from the trial. If the estradiol level is ≥5000 pg/mL, hCG should not be administered and the subject should be discontinued from the trial.

Oocyte retrieval will occur approximately 35-37 hours after hCG administration. On the day after oocyte retrieval, the subject will begin treatment with the Investigational Medicinal Product (IMP), PVR. Following instruction on PVR insertion and removal, the subject will insert the first PVR (PVR1) at the trial site. The PVR will remain in place a minimum of 23 hours/day. The subject will remove PVR1 before fresh embryo transfer and reinsert it after the transfer. Fresh embryo transfer will occur 5 days after oocyte retrieval per the trial site's protocol. The number of embryos to transfer must be guided by the 2017 American Society for Reproductive Medicine (ASRM) and the Society for Assisted Reproductive Technology (SART) guidelines (SART/ASRM 2017): women with the expectation of one or more high-quality embryo(s) available for cryopreservation, and women with previous live birth after an IVF cycle, will have transfer of a single blastocyst. All other women will have transfer of no more than two blastocysts. Additional PVRs will be distributed for weekly insertion, with the second PVR (PVR2) to be inserted at home 7 days following the initial insertion of the first PVR (PVR1), and the third PVR (PVR3) to be inserted either at home or at the site 7 days following the insertion of PVR2.

Two weeks after oocyte retrieval, a blood draw will be performed to measure serum levels of progesterone and β-hCG. Subjects with a β-hCG level <5 mIU/mL will be discontinued from the trial. Those with a β-hCG level ≥5 mIU/mL will insert their next PVR and continue in the trial for up to a total of 10 weeks (up to a total of 10 PVRs). Additional serum pregnancy tests will be performed at 2 weeks + 3-4 days and at 3 weeks. Subjects who are no longer pregnant will be discontinued from the trial. Subjects with positive β-hCG results at 3 weeks will insert PVR4 and receive PVR5 and PVR6 to be inserted weekly.

A TVUS will be performed to document the presence of an intrauterine gestational sac 4 weeks + 3-4 days after oocyte retrieval. If it is determined that the subject has an ectopic pregnancy, the subject will be treated according to the site's standard protocol and will be withdrawn from the trial. Six weeks after oocyte retrieval, a TVUS will be performed to determine the presence and number of gestational sacs with/without fetal heart beat. Pregnant subjects will insert PVR7 and receive additional PVRs to be inserted weekly (PVR8, PVR9, and PVR10). Ten weeks after oocyte retrieval (if the subject is pregnant), an ultrasound (either transvaginal or abdominal) will be performed to determine the number of gestational sacs present with and without fetal heart beat and the estimated gestational age.

Safety will be monitored throughout the trial. Standardized criteria will be applied to AEs of special interest (vaginal bleeding, vaginal pain, and vaginal irritation etc.) to establish grade (intensity). Patient-reported vaginal pain and/or irritation should be recorded as an AE if

considered clinically significant by the physician. The physician can perform an unscheduled pelvic examination at his or her discretion based upon these AEs at any time. A scheduled pelvic examination will be performed at screening, on day 1 of PVR treatment, and at 4 weeks + 3-4 days, 6, 10, and 12 weeks post-oocyte retrieval (Visits 4, 7P, 8, 9 and 10) to document the presence and grade (intensity) of any pain, irritation, abrasions, or lesions on the cervix or vagina and the presence and grade (intensity) of vaginal adhesions using standardized criteria. If any lesions or abrasions are found on the cervix or vagina or vaginal adhesions are noted, another examination will be performed 2-4 days later. Subjects will be followed until the lesions/abrasions resolve or until the final assessment at the End-of-trial visit, whichever comes first. Any clinically significant finding will be reported as an AE.

Post-trial procedures will be performed 2 weeks after the last exposure to IMP (12 weeks after oocyte retrieval). An overview of the trial is provided below:

Screening	Suppression	Stimulation	Oocyte Retrieval	Treatment Period	Post Treatment Period
Consent and Screening	Down-regulation	Visits 1 and 2	Visit 3	Visits 4-9: Day after oocyte retrieval and ongoing pregnancy (~10 weeks) PVR1 through PVR10	Visit 10: End-of-trial visit (2 weeks after last exposure to Investigational Medicinal Product)

NUMBER OF SUBJECTS

Approximately 240 subjects will be needed to complete the controlled ovarian stimulation cycle, undergo oocyte retrieval, be treated with PVR, and receive fresh embryo transfer.

CRITERIA FOR INCLUSION / EXCLUSION

Inclusion Criteria

Subjects must meet the following inclusion criteria:

1. Informed consent signed and dated prior to any trial related procedures.
2. Pre-menopausal females aged 18-34 years old at time of consent.
3. Documentation of a normal uterine cavity by hysteroscopy, hydrosonogram, or hysterosalpingogram within 1 year of screening.
4. Documentation of normal Pap smear test within 24 months of screening.

5. Documentation of negative testing within 6 months of the start of screening for serum Hepatitis B surface antigen, Hepatitis C antibody, human immunodeficiency virus antibody, rapid plasma reagin/venereal disease research laboratory.
6. Documentation of rubella antibody, ABO grouping, Rho typing, and normal prolactin and thyroid function within 6 months of screening.
7. At least 1 cycle without reproductive hormone medication prior to the screening follicle stimulating hormone (FSH) and estradiol blood draw.
8. Tubal, idiopathic, male factor, ovulatory dysfunction, or endometriosis-linked infertility.
9. For fresh sperm: sperm assessed for leukospermia (≥2 million white blood cells/mL or round cells/mL) is required within 2 months of pituitary down regulation OR male partner empirically treated with antibiotics prior to the IVF cycle.
10. Semen analysis within 1 year of screening by standard World Health Organization and/or Kruger criteria. Frozen sperm, including donor sperm, may be used, as long as testing done at the time of freezing meets standard criteria. Male partners with obstructive azoospermia will not be required to have this semen analysis.
11. Able to understand, read, and sign an informed consent after the nature of the trial has been fully explained.
12. Able to complete all trial procedures.

Exclusion Criteria

The presence of any of the following excludes a subject from trial enrollment:

1. Contraindications to the use of progesterone, which include:
    - Known sensitivity to progesterone or related drugs
    - Undiagnosed vaginal bleeding
    - Significant liver dysfunction or disease (including liver function tests >2 times the upper limit of normal)
    - Known or suspected malignancy of the breast or genital organs
    - Active thrombophlebitis or thromboembolic disorders, or a history of hormone-associated thrombophlebitis or thromboembolic disorders
2. Significant psychiatric disease that is not well-controlled.
3. Body mass index >38 kg/m^2.
4. Uncontrolled hypertension (systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg).
5. FSH >15 IU/L during the early follicular phase (Day 2-4). For those subjects with polycystic ovarian syndrome, a Day 2-4 FSH level can be obtained following a progestogen withdrawal or spontaneous menses.

6. Clinically significant gynecologic pathology, such as submucosal fibroids, intramural fibroids >5 cm, communicating hydrosalpinx, uncorrected uterine septum, endometrial cancer or endometrial atypia, scar tissue inside the cavity or poorly developed uterine lining from prior uterine surgery, pelvic tuberculosis, or any other conditions that could adversely affect pregnancy success.
7. Uncontrolled hyperprolactinemia or hypothyroidism.
8. History of pelvic radiation. Subjects with a history of cancer within the last 5 years, except for squamous or basal cell cancer of the skin.
9. Currently pregnant or breastfeeding.
10. Current gonorrhea or chlamydia.
11. History of human immunodeficiency virus/acquired immunodeficiency virus.
12. Known hypersensitivity or previous intolerance to silicone or to any active ingredient or excipients in the medicinal products used in this trial.
13. History of toxic shock syndrome.
14. Known or suspected substance abuse within 1 year prior to screening.
15. Use of any investigational drug or device within 30 days prior to screening.
16. Undergoing donor oocyte cycle, embryo biopsy, or preimplantation genetic testing.
17. History of more than 1 failed fresh IVF cycle. *Note:* an ART cycle is started when a woman begins taking medication to stimulate the ovaries to develop eggs or, if no drugs are given, when the woman begins ovarian follicular monitoring (using ultrasound or blood tests) for natural egg production (Centers for Disease Control, 2005). A failed cycle is defined as having started a cycle and not becoming pregnant or pregnancy loss prior to the 20th week of pregnancy.
18. More than 2 consecutive clinical miscarriages (gestational sac observed on ultrasound).
19. Insulin-sensitizing agents, ART cycle, or ovarian stimulation with gonadotropins within 30 days or clomiphene stimulation within 90 days prior to the screening FSH and estradiol blood draw.
20. Tobacco use within 3 months prior to screening.
21. For fresh sperm: male partners with non-obstructive azoospermia.
22. Any abnormal finding or condition deemed clinically significant by the Investigator on history, screening, physical examination, or pelvic examination that contraindicates pregnancy or the use of progesterone or a vaginal ring, including the presence of any vaginal or cervical abrasions/lesions.
23. Any condition the Investigator believes would interfere with the subject's ability to provide informed consent, to comply with trial instructions, or which might confound the interpretation of the trial results or put the subject at risk.

MEDICINAL PRODUCTS

Investigational Medicinal Product (IMP)

The IMPs in the present trial will be supplied as vaginal rings, which releases an average of 11 mg progesterone/day consistently over 7 days. The progesterone (20% w/w) is in a micronized formulation and dispersed evenly throughout the ring.

Non-Investigational Medicinal Products (NIMPs)

The non-investigational medicinal products (NIMPs) to be used are combined oral contraceptives (CYCLAFEM 1/35, Qualitests Pharmaceuticals), GnRH agonist (LEUPROLIDE ACETATE, Sandoz), HP-hMG (MENOPUR, Ferring Pharmaceuticals), and hCG (NOVAREL, Ferring Pharmaceuticals).

DURATION OF TREATMENT

Eligible subjects will receive up to 10 weeks of progesterone treatment if the subject becomes and remains pregnant. Treatment will be stopped if it is determined the subject has a failed attempt at becoming pregnant or is found to no longer be pregnant.

STATISTICAL METHODS

Primary Analysis

At the final analysis, the cumulative rate of any spontaneous abortion, including spontaneous clinically recognized pregnancy loss and blighted ovum during the trial (up to Week 12 following oocyte retrieval), in subjects treated with PVR following fresh embryo transfer will be estimated (i.e., modified intention-to-treat [mITT] population).

The number and rate of any spontaneous abortions (occurring on or before 12 weeks following oocyte retrieval) for subjects in the mITT cohort will be summarized and the associated two-sided exact 95% confidence interval will be generated. Upon generating the two-sided exact 95% confidence interval, the upper bound of the interval will be assessed for whether it excludes or fails to exclude a spontaneous abortion rate of 15%.

Determination of Sample Size

Statistical simulations have been performed to understand the operating characteristics under varying assumptions for both the sample size of the mITT analysis population and the “true” proportion of spontaneous abortions. For each simulation repetition, a sample of subjects was simulated using the binomial distribution and a given pair of sample size and “true” proportion of spontaneous abortions assumptions. A two-sided 95% exact confidence interval was then created based on the simulated data and the upper bound of this confidence interval was compared to the threshold of 0.15 (corresponding to a spontaneous abortion rate of 15%). If the upper bound of the two-sided 95% exact confidence interval was less than 0.15, the simulation repetition was

declared a "success". If, however, the upper bound of the two-sided 95% exact confidence interval was greater than or equal to 0.15, the simulation repetition was declared a "failure". This process was repeated 10,000 times for each combination of assumed sample size and "true" proportion of spontaneous abortions. The proportion of simulation repetition successes to the total number of simulation repetitions then described the power of the proposed trial given the pair of assumptions.

If the "true" spontaneous abortion rate is 8%, 9%, or 10%, the sample size required to achieve 80% power to exclude the possibility of a 15% spontaneous abortion rate after the use of PVR is 180, 240, or 365, respectively. Taking the middle of this range, a trial with 240 subjects in the mITT analysis population is considered as being adequately powered under a relevant assumption in the target population.

Assessment of Primary and Secondary Endpoints

There are 3 analysis cohorts for this trial. The mITT cohort consists of all subjects who had successful oocyte retrieval, received at least 1 dose of IMP, and had completed fresh embryo transfer. The safety cohort comprises all subjects treated with IMP. The eligible subjects (ES) cohort consists of all subjects who were deemed eligible for trial participation based on inclusion and exclusion criteria at screening and treated with oral contraceptives, leuprolide acetate, or MENOPUR.

The primary objective is to estimate the cumulative rate of any spontaneous abortion, including spontaneous clinically recognized pregnancy loss and blighted ovum during the trial (up to Week 12 following oocyte retrieval) for subjects in the mITT cohort. The number and rates of any spontaneous abortions will be summarized and associated exact 95% confidence intervals will be generated. Furthermore, as part of a Bayesian sensitivity analysis, a 95% credible interval will be generated. The spontaneous abortion rate, biochemical abortion rate, clinical pregnancy rate, and positive β-hCG rate will be similarly analyzed for the mITT and safety cohort, for subjects that had oocyte(s) retrieved. However, for these endpoints, credible intervals will not be derived. Furthermore, safety will be assessed by summarizing treatment-emergent AEs for the safety and ES cohorts. Treatment-emergent AEs will be summarized overall, by grade (intensity), seriousness, and drug relatedness by system organ class and preferred term using the Medical Dictionary for Regulatory Activities. A treatment-emergent AE is any AE that occurs after the start of PVR and through the end of the trial, or a pretreatment AE/medical condition that worsens in intensity after the start of PVR. Furthermore, a separate treatment-emergent AE summary table will be generated for AEs of special interest, such as vaginal pain and irritation, vaginal infection, vaginal bleeding/spotting, vaginal hemorrhage, vaginal adhesions and vaginal or cervical abrasions and lesions. These events will also be further analyzed by grade (intensity). Tolerability for the safety cohort will be assessed by summarizing the total number of subjects who prematurely discontinued PVR and the associated reasons for discontinuation. This summary will be based on the safety cohort.

For the safety and ES cohorts, the number of subjects with abnormal clinical laboratory and vital sign assessments will be summarized.

TABLE OF CONTENTS

SYNOPSIS **2**

LIST OF TABLES **18**

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS **19**

1 INTRODUCTION **20**
1.1 Background 20
1.2 Scientific Justification for Conducting the Trial 21
1.3 Benefit / Risk Aspects 22

2 TRIAL OBJECTIVES AND ENDPOINTS **23**
2.1 Objectives 23
2.2 Endpoints 23

3 INVESTIGATIONAL PLAN **25**
3.1 Overall Trial Design 25
3.1.1 Trial Design Diagram 25
3.1.2 Overall Design and Control Methods 25
3.1.3 Trial Schedule 27
3.2 Planned Number of Trial Sites and Subjects 27
3.3 Interim Analysis 27
3.4 Data Monitoring Committee (DMC) 27
3.5 Discussion of Overall Trial Design and Choice of Control Groups 27
3.5.1 Trial Design 27
3.5.2 Selection of Endpoints 27
3.5.3 Blinding 28
3.5.4 Selection of Doses in the Trial 28
3.5.5 Selection and Timing of Dose for Each Subject 28
3.5.6 Discontinuation and Trial Stopping Criteria 28
3.5.7 Follow-up Procedures 29

4 SELECTION OF TRIAL POPULATION **30**
4.1 Trial Population 30
4.1.1 Inclusion Criteria 30
4.1.2 Exclusion Criteria 30
4.2 Method of Assigning Subjects to Treatment Groups 32
4.2.1 Recruitment 32
4.2.2 Randomization 32
4.3 Restrictions 32
4.3.1 Prior and Concomitant Therapies 32
4.3.2 Prohibited Therapy 32
4.4 Withdrawal Criteria 33

5 TREATMENTS **34**
5.1 Treatments Administered 34
5.1.1 Investigational Medicinal Product (IMP) 34
5.1.2 Non-Investigational Medicinal Product (NIMP) 34
5.2 Characteristics and Source of Supply 35
5.3 Packaging and Labelling 35

5.4 Conditions for Storage and Use ... 36
5.5 Blinding / Unblinding ... 36
5.5.1 Blinding ... 36
5.5.2 Unblinding of Individual Subject Treatment ... 36
5.6 Treatment Compliance ... 36
5.6.1 Dispensing and Accountability ... 36
5.6.2 Assessment of Compliance ... 37
5.7 Auxiliary Supplies ... 37
5.8 Return and Destruction of Medicinal Products ... 37

6 TRIAL PROCEDURES ... 38
6.1 Screening and Ovarian Suppression (Down-regulation) ... 41
6.2 Ovarian Stimulation and Oocyte Retrieval ... 42
6.2.1 Visit 1: Start of Ovarian Stimulation ... 42
6.2.2 Visit 2: End of Ovarian Stimulation ... 42
6.2.3 Visit 3: Oocyte Retrieval ... 43
6.3 Treatment with PVR ... 43
6.3.1 Visit 4: Initiation of Treatment with PVR ... 43
6.3.2 Visit 5: Embryo Transfer ... 44
6.3.3 Visit 6: 2 Weeks After Oocyte Retrieval ... 45
6.3.4 Visit 6P: Procedural Visit ... 45
6.3.5 Visit 7: Week 5 of Pregnancy (3 Weeks After Oocyte Retrieval) ... 46
6.3.6 Visit 7P: Procedural Visit ... 46
6.3.7 Visit 8: Week 8 of Pregnancy (6 Weeks After Oocyte Retrieval) ... 47
6.3.8 Visit 9: Week 12 of Pregnancy (10 Weeks After Oocyte Retrieval) / Early-withdrawal Visit ... 48
6.4 End-of-trial ... 48

7 TRIAL ASSESSMENTS ... 50
7.1 Assessments Related to Primary Endpoint ... 50
7.1.1 Pregnancy Monitoring ... 50
7.1.1.1 β-hCG Test ... 50
7.1.1.2 Transvaginal Ultrasound ... 50
7.1.1.3 Ectopic and Heterotopic Pregnancies ... 50
7.1.2 Spontaneous Abortion ... 50
7.2 Assessments Related to Secondary Endpoints ... 50
7.2.1 Positive β-hCG ... 50
7.2.2 Clinical Pregnancy ... 51
7.2.3 Biochemical Abortion ... 51
7.2.4 Bleeding Log ... 51
7.2.5 Vaginal Hemorrhage ... 51
7.2.6 Clinical Laboratory Variables ... 51
7.2.7 Vital Signs ... 52
7.2.8 Pelvic Examination ... 52
7.2.9 Adverse Events ... 52
7.2.9.1 Adverse Events of Special Interest ... 52
7.3 Other Assessments ... 53
7.3.1 Demographics ... 53

7.3.2 Medical/Gynecological History ... 53
7.3.3 Physical Examination ... 53
7.3.4 Height, Weight, and Body Mass Index Calculation ... 53
7.3.5 Pelvic Examination and Pap Smear at Screening ... 53
7.3.6 PVR Diary ... 53
7.3.7 Number and Size of Follicles ... 54
7.3.8 Oocyte Retrieval ... 54
7.3.9 Endometrial Thickness ... 54
7.3.10 Embryo Transfer ... 54
7.3.11 Concomitant Medication ... 54

8 ADVERSE EVENTS ... 55
8.1 Adverse Event Definition ... 55
8.2 Collection and Recording of Adverse Events ... 55
8.2.1 Collection of Adverse Events ... 55
8.2.2 Recording of Adverse Events ... 56
8.3 Adverse Events of Special Interest ... 58
8.3.1 Vaginal Pain and Irritation ... 59
8.3.2 Vaginal or Cervical Abrasions and Lesions ... 59
8.3.3 Vaginal Adhesions ... 59
8.3.4 Vaginal Infection ... 59
8.3.5 Vaginal Bleeding/Spotting ... 59
8.3.6 Vaginal Hemorrhage ... 59
8.3.7 Pregnancy Losses ... 59
8.4 Serious Adverse Events ... 60
8.4.1 Serious Adverse Event Definition ... 60
8.4.2 Collection, Recording and Reporting of Serious Adverse Events ... 61
8.5 Follow-up of Adverse Events and Serious Adverse Events ... 62
8.5.1 Follow-up of Adverse Events with Onset during the Trial ... 62
8.5.2 Follow-up of Adverse Events on Non-Investigational Medicinal Products During the Trial ... 62
8.5.3 Collection of Serious Adverse Events with Onset after Last Visit in the Trial ... 62

9 STATISTICAL METHODS ... 63
9.1 Primary Analysis ... 63
9.2 Determination of Sample Size ... 63
9.3 Subject Disposition ... 64
9.4 Protocol Deviations ... 64
9.5 Analysis Sets ... 64
9.5.1 mITT Cohort ... 64
9.5.2 Safety Cohort ... 64
9.5.3 Eligible Subjects (ES) Cohort ... 65
9.6 Trial Population ... 65
9.6.1 Demographics and other Baseline Characteristics ... 65
9.6.2 Medical History, Concomitant Medication and Other Safety Evaluations ... 65
9.6.3 Prior and Concomitant Medications ... 65
9.7 Endpoint Assessments ... 66
9.7.1 General Considerations ... 66

9.7.2 Primary Endpoint 66
9.7.3 Secondary Endpoints 66
9.7.3.1 Spontaneous Abortion within 6 and 10 Weeks of Oocyte Retrieval 66
9.7.3.2 Biochemical Abortions within 6 and 10 Weeks of Oocyte Retrieval 66
9.7.3.3 Ectopic and Heterotopic Pregnancies 67
9.7.3.4 Positive β-hCG 67
9.7.3.5 Clinical Pregnancy 67
9.7.4 Other Assessments 67
9.7.4.1 Number and Size of Follicles during Stimulation 67
9.7.4.2 E2 and Progesterone Profiles 68
9.7.4.3 Oocytes 68
9.7.4.4 Characterization of Fertilized Oocytes one Day (Day 1) after Oocyte Retrieval 68
9.7.4.5 Quality of Blastocysts 5 Days (Day 5) after Oocyte Retrieval 68
9.7.4.6 Endometrial Thickness 70
9.8 Extent of Exposure and Treatment Compliance 71
9.8.1 PVR 71
9.8.2 Oral Contraceptives 71
9.8.3 MENOPUR, Leuprolide Acetate, and hCG 71
9.9 Safety 71
9.9.1 General Considerations 71
9.9.2 Adverse Events 72
9.9.2.1 Treatment-Emergent AEs of Special Interest 72
9.9.3 Safety Laboratory Variables 72
9.9.4 Vital Signs 73
9.9.5 Bleeding Log 73
9.9.6 Vaginal Hemorrhage 73
9.9.7 Pelvic Examination 73
9.10 Interim Analyses 73

10 DATA HANDLING 74
10.1 Source Data and Source Documents 74
10.2 eCRF/Case Report Form 75
10.3 Data Management 75
10.4 Provision of Additional Information 76

11 MONITORING PROCEDURES 77
11.1 Periodic Monitoring 77
11.2 Audit and Inspection 77
11.3 Confidentiality of Subject Data 77

12 CHANGES IN THE CONDUCT OF THE TRIAL 79
12.1 Protocol Amendments 79
12.2 Deviations from the Protocol 79
12.3 Premature Trial Termination 79

13 REPORTING AND PUBLICATION 80
13.1 Clinical Trial Report 80
13.2 Confidentiality and Ownership of Trial Data 80
13.3 Publications and Public Disclosure 80

13.3.1 Publication Policy 80
13.3.2 Public Disclosure Policy 81

14 ETHICAL AND REGULATORY ASPECTS 82
14.1 Institutional Review Board 82
14.2 Regulatory Authority Authorization/Approval/Notification 82
14.3 End-of-Trial and End-of-Trial Notification 82
14.4 Ethical Conduct of the Trial 82
14.5 Subject Information and Consent 82
14.6 Subject Participation Card 83
14.7 Compliance Reference Documents 83

15 LIABILITIES AND INSURANCE 84
15.1 ICH-GCP Responsibilities 84
15.2 Liabilities and Insurance 84

16 ARCHIVING 85
16.1 Investigator File 85
16.2 Trial Master File 85

17 REFERENCES 86

APPENDICES 87
Appendix 1 Sample Subject Instructions For Use 87
Appendix 2 Pelvic Examination, Grade, and Criteria 90
Appendix 3 Assessment of AEs of Special Interest: Vaginal Pain and Vaginal Irritation 93
Appendix 4 Bleeding Log 94
Appendix 5 Scoring of Bleeding Log Information 95
Appendix 6 Primary Analysis Simulation Code and the Sensitivity Analysis Operating Characteristics 96

LIST OF TABLES

Table 3-1 Trial Flow Overview 25
Table 5-1 Non-investigational Medicinal Products 34
Table 5-2 Characteristics of Medicinal Products 35
Table 5-3 Packaging of Medicinal Products 36
Table 6-1 Trial Schedule 39
Table 9-1 Power Achieved over Varying Sample Sizes and Assumed Spontaneous Abortion Rates 64
Table 9-2 Good-Quality Blastocysts 70

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
ART	Assisted Reproductive Technology
eCRF	electronic case report form
EOT	End-of-trial
ES	eligible subjects
ET	embryo transfer
EudraCT	European Union Clinical Trial Database
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GnRH	gonadotrophin-releasing hormone
hCG	human chorionic gonadotropin
HP-hMG	highly purified, human menopausal gonadotropin
HPV	human papilloma virus
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRT	interactive response technology
IVF	in vitro fertilization
LH	luteinizing hormone
mITT	modified intention-to-treat
NIMP	Non-Investigational Medicinal Product
P	procedural visit
PVR	progesterone vaginal ring
OR	oocyte retrieval
OS	ovarian stimulation
SAE	serious adverse event
TVUS	transvaginal ultrasound

1 INTRODUCTION

1.1 Background

Successful human reproduction is dependent upon the influence of progesterone on endometrial structure and receptivity. Once the corpus luteum is formed after ovulation, it begins to secrete progesterone, which is necessary and sufficient to decidualize the endometrium to facilitate implantation. If conception and implantation occur, increasing concentrations of human chorionic gonadotropin (hCG) drive continued secretion of progesterone from the corpus luteum, which is critical for the maintenance of early pregnancy and the endometrium (Penzias, 2002). Progesterone continues to be produced by the corpus luteum until the seventh or eighth week of gestation, at which time the placenta becomes the primary site of production for the remainder of pregnancy.

Unfortunately, not all women of reproductive age are able to become pregnant or maintain a pregnancy; indeed, 12 percent of women of reproductive age in the United States have received an infertility service at some time in their lives. The administration of exogenous progesterone to support luteal function has been utilized in the treatment of infertility, particularly with assisted reproductive technology (ART). Assisted reproductive technology generally involves the surgical removal of eggs from a woman's ovaries, fertilizing them with sperm in the laboratory, and then returning them to either the donor woman's or another woman's uterus (Centers for Disease Control, 2005). For many women, in conjunction with ART, steps must be taken to prime the uterus for implantation and to sustain the pregnancy after implantation. Many tools have been developed to aid in this process.

In the middle of the 1980s, gonadotrophin-releasing hormone (GnRH) agonists were incorporated into ovarian stimulation regimens and are associated with improved outcomes after in vitro fertilization (IVF) and other ARTs. These GnRH agonists work by suppressing the pituitary and preventing premature surges of endogenous luteinizing hormone (LH) during IVF cycles and allowing time for a larger number of oocytes to reach maturity prior to harvesting. However, GnRH agonists inhibit the corpora lutea in these cycles and may create an iatrogenic luteal phase defect. Use of a GnRH agonist causes suppression of pituitary LH secretion for as long as 10 days after the last dose, and pituitary function may not return completely until 2-3 weeks after the end of therapy. Without this LH signal, the corpus luteum may be dysfunctional, and subsequent progesterone and estrogen secretion may be abnormal, compromising endometrial receptivity and potentially leading to decreased implantation and pregnancy rates (Pritts, 2002).

Various hormones, including estrogens, progesterone, and hCG have been used during the luteal phase and beyond in IVF cycles for luteal phase support. A 1994 meta-analysis showed that the use of hCG or progesterone led to significantly higher pregnancy rates than placebo (Soliman, 1994). Most treatment protocols advocate the use of progesterone throughout the first trimester of pregnancy, since corpus luteum activity has been demonstrated up to Week 10 of pregnancy, although progesterone supplementation continuing beyond a positive serum pregnancy test may not be needed. The goal of progesterone supplementation is to assist a corpus luteum that may have become compromised during ovulation induction or oocyte retrieval (Penzias, 2002).

Moreover, the vaginal route of progesterone administration has been shown to allow effective targeted delivery for various indications, including supplementation of corpus luteal function. The vaginal route offers several important advantages over other methods: it is convenient and acceptable for many patients, is not painful, does not require any special equipment, systemic levels are low, and it rarely produces allergic or other adverse reactions. Therefore, a flexible, non-degradable progesterone vaginal ring (PVR) has been developed, releasing an average of 11 mg progesterone/day consistently over 7 days. The progesterone (20% w/w) is in a micronized formulation and dispersed evenly throughout the ring.

1.2 Scientific Justification for Conducting the Trial

In a pivotal phase 3 trial (Teva Women's Health, Inc. Study DR-PGN-302) evaluating the efficacy and safety of a progesterone vaginal ring (PVR) used for luteal phase support in women undergoing IVF, the primary endpoint was clinical pregnancy rate at 8 and 12 weeks of pregnancy. Once weekly PVR was statistically non-inferior to the active comparator, daily 8% progesterone vaginal gel, in women 18-34 years of age. Secondary efficacy analyses included evaluations of live birth rate, cycle cancellation rate, rate of spontaneous abortion, rate of biochemical pregnancy, and rate of ectopic pregnancy for each treatment group. These rates were similar between the 2 active treatment groups and consistent with reported background rates. Weekly PVR insertion appeared to be safe and well tolerated. Adverse events (AEs) and serious adverse events (SAEs) were similar for both active treatment groups, and no significant safety trends were noted for PVR. Treatment-related AEs were generally similar between the 2 active treatment groups and consistent with the known safety profile of progesterone. Rates of subject discontinuation due to an AE were similar between the treatment groups. AEs related to vaginal bleeding were similar between the 2 active treatment groups. No subject discontinued because of vaginal bleeding, and no subject was switched to an alternative progesterone product because of a bleeding issue. There were no increased rates of cervical/vaginal abrasions or irritation associated with use of a vaginal ring compared with vaginal gel.

Manufacturing enhancements for the PVR were implemented subsequent to the pivotal phase 3 trial. Therefore, a bioequivalence trial was conducted to compare the PVR manufactured using the new process to the ring manufactured by the legacy process (the phase 3 clinical trial material). The results from the pharmacokinetic trial (DR201-BE-10021) demonstrated that the PVR manufactured with the new process was bioequivalent to the PVR produced from the legacy process. The safety data indicated that both rings were similarly safe and well tolerated by healthy, postmenopausal female subjects who were pretreated with estrogen.

The present trial assesses the safety and tolerability of the PVR manufactured with the new process when used for luteal phase support in women undergoing ART. While the design of the proposed trial is similar to that of the pivotal phase 3 trial for the PVR, changes to the way in which AEs are collected and scored have been implemented as requested by the Agency.

1.3 Benefit / Risk Aspects

The benefit/risk aspects are expected to be similar to what is outlined in the Investigator's Brochure for the Investigational Medicinal Product (IMP), PVR, and in the appropriate package inserts for the non-investigational medicinal products: oral contraceptives, leuprolide acetate, hCG, and MENOPUR (menotropins for injection [package insert], 2016). The PVR offers patients a convenient, once-weekly option for luteal phase support as an alternative to twice-daily dosing or 3-times daily dosing of the progesterone vaginal insert, once-daily dosing of the progesterone vaginal gel, or once-daily intramuscular injection of progesterone in oil that are in current clinical use in the United States.

2 TRIAL OBJECTIVES AND ENDPOINTS

In this safety trial the assessment of the trial will be on the totality of safety information collected. Hence, the purpose of categorizing the endpoints as primary and secondary is for prioritising the endpoints of interest rather than tying the trial's success to the outcome of the primary objective.

2.1 Objectives

Primary Objective

- To estimate the cumulative rate of any spontaneous abortion, including spontaneous clinically recognized pregnancy loss and blighted ovum during the trial (up to Week 12 following oocyte retrieval), in subjects treated with PVR following fresh embryo transfer.

Secondary Objectives

- To describe the cumulative rate of spontaneous abortions determined at 6 and 10 weeks post-oocyte retrieval, including spontaneous clinically recognized pregnancy loss and blighted ovum, in all subjects treated with PVR.
- To describe the cumulative rate of biochemical abortions determined at 6 and 10 weeks post-oocyte retrieval in all subjects treated with PVR.
- To describe the rate of ectopic and heterotopic pregnancy in all subjects treated with PVR following oocyte retrieval.
- To describe the safety of PVR through the collection of clinical laboratory tests and vital signs in all subjects treated with PVR.
- To assess the safety and tolerability of PVR in all subjects treated with PVR.
- To determine the positive β-hCG rate of subjects treated with PVR following oocyte retrieval.
- To determine the clinical pregnancy rate of subjects treated with PVR following oocyte retrieval.

2.2 Endpoints

Primary Endpoint

- Cumulative rate of any spontaneous abortion occurring on or before 12 weeks following oocyte retrieval in all subjects treated with PVR and undergoing fresh embryo transfer. *Note:* spontaneous abortion is defined as two positive β-hCG tests occurring at least two days apart on or after 2 weeks post-oocyte retrieval, but followed by observation of any empty intrauterine gestational sac (blighted ovum), intrauterine gestation without a fetal heart beat, or absence of viable fetuses, as documented by transvaginal ultrasound (TVUS).

Secondary Endpoints

- Cumulative rate of spontaneous abortions determined at 6 and 10 weeks post-oocyte retrieval in all subjects treated with PVR.
- Cumulative rate of biochemical abortions determined at 6 and 10 weeks post-oocyte retrieval in all subjects treated with PVR. Biochemical abortion is defined as a positive β-hCG test at 2 weeks and 2 weeks + 3-4 days post-oocyte retrieval, but followed by no observed gestational sac on a later TVUS, or followed by a negative β-hCG test.
- Rate of ectopic and heterotopic pregnancies in all subjects treated with PVR following oocyte retrieval.
- Rate of abnormal findings in clinical laboratory tests and vital signs for all subjects treated with PVR.
- Frequency, intensity/grade, seriousness, and relatedness of adverse events (AEs) for all subjects treated with PVR.
- Frequency, intensity/grade of vaginal bleeding/spotting, vaginal hemorrhage, pain, vaginal infection, and vaginal irritation for all subjects treated with PVR.
- Frequency, intensity/grade, seriousness, and relatedness of AEs associated with vaginal and cervical abrasions and lesions and with vaginal adhesions for all subjects treated with PVR.
- Frequency and reason for PVR discontinuation.
- Positive β-hCG rate (positive serum β-hCG test) at 2 weeks and 2 weeks + 3-4 days post-oocyte retrieval in all subjects treated with PVR.
- Clinical pregnancy rate (TVUS showing at least 1 intrauterine gestational sac with fetal heart beat) at 6 and 10 weeks post-oocyte retrieval in all subjects treated with PVR.

3 INVESTIGATIONAL PLAN

3.1 Overall Trial Design

3.1.1 Trial Design Diagram

A trial flow overview is provided in Table 3-1.

Table 3-1 Trial Flow Overview

Screening	Suppression	Stimulation	Oocyte Retrieval	Treatment Period	Post Treatment Period
Consent and Screening	Down-regulation	Visits 1 and 2	Visit 3	Visits 4-9: Day after oocyte retrieval and ongoing pregnancy (~10 weeks) PVR1 through PVR10	Visit 10: End-of-trial visit (2 weeks after last exposure to Investigational Medicinal Product)

3.1.2 Overall Design and Control Methods

This is an open-label, single-arm, safety trial of PVR for luteal phase support in women undergoing IVF with fresh oocytes. Women between the ages of 18 and 34 years with tubal, idiopathic, male factor, ovulatory dysfunction, or endometriosis-linked infertility, who agree to be considered for inclusion in the trial, will be invited to be seen at the trial site.

Once informed consent is obtained, eligible subjects will be started on an ovarian down-regulation / suppression protocol utilizing combined oral contraceptives supplied by the site for ≥14 days to ≤21 days (based upon the site standard of care), with leuprolide acetate at a dose of 0.1 mL (500 µg)/day beginning 4 days prior to the last birth control pill and for ≥10 days to ≤20 days; ovarian suppression is to begin in the cycle immediately prior to the ovarian stimulation cycle. After suppression, an ovarian stimulation protocol will begin on the second or third day after the start of menses with a reduction in leuprolide acetate dose to 0.05 mL (250 µg/day) followed by an individually determined ovarian stimulation protocol with highly purified, human menopausal gonadotropin (HP-hMG; MENOPUR) at an initial dose of 225 IU/day for 5 days according to label. Based on clinical monitoring, subsequent dosing should be adjusted according to individual subject response. Dose adjustments should not be made more frequently than once every two days and should not exceed 150 IU per adjustment. The maximum daily dose of MENOPUR should not exceed 450 IU and the minimum daily dose should not be lower than 75 IU. MENOPUR dosing should not continue for >20 days and coasting is not allowed. Subjects will be monitored to determine when to trigger ovulation with hCG. A TVUS will be performed to assess follicle size and serum estradiol levels will be determined. A subject must have at least 2 follicles ≥17 mm (mean of 2 dimensions) to receive the hCG trigger. Subjects who do not reach this threshold after 20 days of stimulation are to be discontinued from the trial. If the estradiol level is ≥5000 pg/mL, hCG should not be administered and the subject should be discontinued from the trial.

Oocyte retrieval will occur approximately 35-37 hours after hCG administration. On the day after oocyte retrieval, the subject will begin treatment with the IMP, PVR. Following instruction on PVR insertion and removal (see Appendix 1), the subject will insert the first PVR (PVR1) at the trial site The PVR will remain in place a minimum of 23 hours/day. The subject will remove PVR1 before embryo transfer and reinsert it after the transfer. Fresh embryo transfer will occur 5 days after oocyte retrieval per the trial site's protocol. The number of embryos to transfer must be guided by the 2017 American Society for Reproductive Medicine (ASRM) and the Society for Assisted Reproductive Technology (SART) guidelines (SART/ASRM 2017): women with the expectation of one or more high-quality embryo(s) available for cryopreservation, and women with previous live birth after an IVF cycle, will have transfer of a single blastocyst. All other women will have transfer of no more than two blastocysts. Additional PVRs will be distributed for weekly insertion, with the second PVR (PVR2) to be inserted at home 7 days following the initial insertion of the first PVR (PVR1), and the third PVR (PVR3) to be inserted either at home or at the site 7 days following the insertion of PVR2.

Two weeks after oocyte retrieval, a blood draw will be performed to measure serum levels of progesterone and β-hCG. Subjects with a β-hCG level <5 mIU/mL will be discontinued from the trial. Those with a β-hCG level ≥5 mIU/mL will insert their next PVR and continue in the trial for up to a total of 10 weeks (up to a total of 10 PVRs). Additional serum pregnancy tests will be performed at 2 weeks + 3-4 days and at 3 weeks. Subjects who are no longer pregnant will be discontinued from the trial. Subjects with positive β-hCG results at 3 weeks will insert PVR4 and receive PVR5 and PVR6 to be inserted weekly.

A TVUS will be performed to document the presence of an intrauterine gestational sac 4 weeks + 3-4 days after oocyte retrieval. If it is determined that the subject has an ectopic pregnancy, the subject will be treated according to the site's standard protocol and will be withdrawn from the trial. Six weeks after oocyte retrieval, a TVUS will be performed to determine the presence and number of gestational sacs with/without fetal heart beat. Pregnant subjects will insert PVR7 and receive additional PVRs to be inserted weekly (PVR8, PVR9, and PVR10). Ten weeks after oocyte retrieval (if the subject is pregnant), an ultrasound (either transvaginal or abdominal) will be performed to determine the number of gestational sacs present with and without fetal heart beat and the estimated gestational age.

Safety will be monitored throughout the trial. Standardized criteria will be applied to AEs of special interest (vaginal bleeding, vaginal pain, and vaginal irritation etc., see section 8.3) to establish grade (intensity). Patient-reported vaginal pain and/or irritation (Appendix 3) should be recorded as an AE if considered clinically significant by the physician. The physician can perform an unscheduled pelvic examination at his or her discretion based upon these AEs at any time (see Appendix 2). A scheduled pelvic examination will be performed at screening, on day 1 of PVR treatment, and 4 weeks + 3-4 days, 6, 10, and 12 weeks post-oocyte retrieval (Visits 4, 7P, 8, 9 and 10) to document the presence and grade (intensity) of any pain, irritation, abrasions, or lesions on the cervix or vagina and the presence and grade (intensity) of vaginal adhesions using standardized criteria (Appendix 2). If any lesions or abrasions are found on the cervix or vagina or vaginal adhesions are

noted, another examination will be performed 2-4 days later. Subjects will be followed until the lesions/abrasions resolve or until the final assessment at the End-of-trial visit, whichever comes first. Any clinically significant finding will be reported as an AE.

Post-trial procedures will be performed 2 weeks after the last exposure to investigational medicinal product (IMP) (12 weeks after oocyte retrieval).

3.1.3 Trial Schedule

The estimated first subject, first visit is Q3 2018 with last subject, last visit during Q3 2019.

3.2 Planned Number of Trial Sites and Subjects

Approximately 240 subjects will be needed to complete the controlled ovarian stimulation cycle, undergo oocyte retrieval, be treated with PVR, and receive fresh embryo transfer.

3.3 Interim Analysis

No interim analysis is planned.

3.4 Data Monitoring Committee (DMC)

No data monitoring committee is planned.

3.5 Discussion of Overall Trial Design and Choice of Control Groups

3.5.1 Trial Design

This is an open-label, single-arm trial of progesterone supplementation (luteal phase support) in women undergoing IVF with fresh oocytes. Each trial center will follow the trial center's standard practice for ART unless otherwise noted in this protocol. On the day after oocyte retrieval, the subject will begin treatment with the IMP, PVR. Embryo transfer will occur 5 days after oocyte retrieval. A serum pregnancy test will be conducted 2 weeks after the oocyte retrieval. Subjects with a β-hCG level <5 mIU/mL will be discontinued from the trial. Those with a β-hCG level ≥5 mIU/mL will continue dosing with PVR for up to a total of 10 weeks.

The primary objective is to estimate the cumulative rate of any spontaneous abortion, including spontaneous clinically recognized pregnancy loss and blighted ovum during the trial (up to Week 12 following oocyte retrieval), in subjects treated with PVR following fresh embryo transfer. Approximately 240 subjects will be enrolled in the trial in order to ensure that 215 subjects undergo fresh embryo transfer.

3.5.2 Selection of Endpoints

The endpoints in this trial (rate of any spontaneous abortion, biochemical abortion, ectopic and heterotopic pregnancies as well as rate of clinical pregnancy and positive β-hCG) are typical endpoints to demonstrate the safety of products used for progesterone supplementation in women undergoing ART. AEs of special interest due to the vaginal administration are also included as secondary endpoints, and cover vaginal bleeding/spotting, vaginal hemorrhage, pain, vaginal

infection, vaginal irritation, vaginal and cervical abrasions and lesions, and vaginal adhesions. Finally, typical safety endpoints such as laboratory results and vital signs are also included.

3.5.3 Blinding

This is an open-label trial.

3.5.4 Selection of Doses in the Trial

Subjects will be instructed to insert the first PVR on the day after oocyte retrieval, which contains 11 mg progesterone/day and remains in place a minimum of 23 hours/day for 7 days.

3.5.5 Selection and Timing of Dose for Each Subject

A new PVR will be inserted every 7 days, with up to 10 PVRs used through Week 12 of pregnancy (10 weeks post-oocyte retrieval).

3.5.6 Discontinuation and Trial Stopping Criteria

Discontinuation Criteria

Two days prior to oocyte retrieval, a TVUS will be performed to assess follicle size. A subject must have at least 2 follicles ≥17 mm (mean of 2 dimensions) to receive the hCG trigger. Subjects who do not reach this threshold after 20 days of stimulation are to be discontinued from the trial. If the estradiol level is ≥5000 pg/mL, hCG should not be administered and the subject should be discontinued from the trial.

A serum pregnancy test will be conducted 2, 2.5, and 3 weeks after the oocyte retrieval. Subjects with a β-hCG level <5 mIU/mL will be discontinued from the trial. A TVUS will be performed to document the presence of an intrauterine gestational sac 4.5 weeks after oocyte retrieval. If it is determined that the subject has an ectopic pregnancy, the subject will be treated according to the site's standard protocol and will be withdrawn from the trial.

Subjects who discontinue the trial are to complete an Early Withdrawal Visit (section 6.3.8) no later than 1 week after the last dose of the IMP. An End of Trial Visit (section 6.4) is required 2 weeks after the last dose of IMP.

Trial Stopping Criteria

Occurrence of the following may warrant consideration of trial termination:

Life-threatening SAEs with suspected causality to the IMP, but not limited to those with grade 4 as detailed in Appendix 2 and Appendix 3.

Ferring's internal Safety Committee will review each occurrence and provide a recommendation as to whether to discontinue the trial. The responsibilities and composition of the internal Safety Committee are provided in a separate charter document, available before the first subject's first visit.

3.5.7 Follow-up Procedures

Two weeks after the last exposure to the IMP, subjects will return for an End-of-trial Visit. Physical and pelvic examinations will be performed; vital signs will be measured; blood and urine will be collected for hematology, chemistry and urinalysis; and AEs will be assessed. If any lesions or abrasions are found on the cervix or vagina or vaginal adhesions are noted, another examination will be performed 2-4 days later until the lesions/abrasions or vaginal adhesions resolve or until the final assessment at the End-of-trial visit, whichever comes first. Vaginal adhesions observed can be surgically addressed based on the Investigator's judgement.

4 SELECTION OF TRIAL POPULATION

4.1 Trial Population

4.1.1 Inclusion Criteria

Subjects must meet the following inclusion criteria:

1. Informed consent signed and dated prior to any trial related procedures.
2. Pre-menopausal females aged 18-34 years old at time of consent.
3. Documentation of a normal uterine cavity by hysteroscopy, hydrosonogram, or hysterosalpingogram within 1 year of screening.
4. Documentation of normal Pap smear test within 24 months of screening.
5. Documentation of negative testing within 6 months of the start of screening for serum Hepatitis B surface antigen, Hepatitis C antibody, human immunodeficiency virus antibody, rapid plasma reagin/venereal disease research laboratory.
6. Documentation of rubella antibody, ABO grouping, Rho typing, and normal prolactin and thyroid function within 6 months of screening.
7. At least 1 cycle without reproductive hormone medication prior to the screening follicle stimulating hormone (FSH) and estradiol blood draw.
8. Tubal, idiopathic, male factor, ovulatory dysfunction, or endometriosis-linked infertility.
9. For fresh sperm: sperm assessed for leukospermia (≥2 million white blood cells/mL or round cells/mL) is required within 2 months of pituitary down regulation OR male partner empirically treated with antibiotics prior to the IVF cycle.
10. Semen analysis within 1 year of screening by standard World Health Organization and/or Kruger criteria. Frozen sperm, including donor sperm, may be used, as long as testing done at the time of freezing meets standard criteria. Male partners with obstructive azoospermia will not be required to have this semen analysis.
11. Able to understand, read, and sign an informed consent after the nature of the trial has been fully explained.
12. Able to complete all trial procedures.

4.1.2 Exclusion Criteria

The presence of any of the following excludes a subject from trial enrollment:

1. Contraindications to the use of progesterone, which include:
    - Known sensitivity to progesterone or related drugs
    - Undiagnosed vaginal bleeding
    - Significant liver dysfunction or disease (including liver function tests >2 times the upper limit of normal)

- Known or suspected malignancy of the breast or genital organs
- Active thrombophlebitis or thromboembolic disorders, or a history of hormone-associated thrombophlebitis or thromboembolic disorders

2. Significant psychiatric disease that is not well-controlled.
3. Body mass index >38 kg/m^2.
4. Uncontrolled hypertension (systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg).
5. FSH >15 IU/L during the early follicular phase (Day 2-4). For those subjects with polycystic ovarian syndrome, a Day 2-4 FSH level can be obtained following a progestogen withdrawal or spontaneous menses.
6. Clinically significant gynecologic pathology, such as submucosal fibroids, intramural fibroids >5 cm, communicating hydrosalpinx, uncorrected uterine septum, endometrial cancer or endometrial atypia, scar tissue inside the cavity or poorly developed uterine lining from prior uterine surgery, pelvic tuberculosis, or any other conditions that could adversely affect pregnancy success.
7. Uncontrolled hyperprolactinemia or hypothyroidism.
8. History of pelvic radiation. Subjects with a history of cancer within the last 5 years, except for squamous or basal cell cancer of the skin.
9. Currently pregnant or breastfeeding.
10. Current gonorrhea or chlamydia.
11. History of human immunodeficiency virus/acquired immunodeficiency virus.
12. Known hypersensitivity or previous intolerance to silicone or to any active ingredient or excipients in the medicinal products used in this trial.
13. History of toxic shock syndrome.
14. Known or suspected substance abuse within 1 year prior to screening.
15. Use of any investigational drug or device within 30 days prior to screening.
16. Undergoing donor oocyte cycle, embryo biopsy, or preimplantation genetic testing.
17. History of more than 1 failed fresh IVF cycle. *Note:* an ART cycle is started when a woman begins taking medication to stimulate the ovaries to develop eggs or, if no drugs are given, when the woman begins ovarian follicular monitoring (using ultrasound or blood tests) for natural egg production (Centers for Disease Control, 2005). A failed cycle is defined as having started a cycle and not becoming pregnant or pregnancy loss prior to the 20th week of pregnancy.
18. More than 2 consecutive clinical miscarriages (gestational sac observed on ultrasound).
19. Insulin-sensitizing agents, ART cycle, or ovarian stimulation with gonadotropins within 30 days or clomiphene stimulation within 90 days prior to the screening FSH and estradiol blood draw.
20. Tobacco use within 3 months prior to screening.

21. For fresh sperm: male partners with non-obstructive azoospermia.
22. Any abnormal finding or condition deemed clinically significant by the Investigator on history, screening, physical examination, or pelvic examination that contraindicates pregnancy or the use of progesterone or a vaginal ring, including the presence of any vaginal or cervical abrasions/lesions.
23. Any condition the Investigator believes would interfere with the subject's ability to provide informed consent, to comply with trial instructions, or which might confound the interpretation of the trial results or put the subject at risk.

4.2 Method of Assigning Subjects to Treatment Groups

4.2.1 Recruitment

Sites will recruit subjects based on the inclusion/exclusion criteria and local recruitment practices. Recruitment materials cannot be used prior to Institutional Review Board (IRB) approval.

4.2.2 Randomization

This trial is not randomized.

4.3 Restrictions

4.3.1 Prior and Concomitant Therapies

Any concomitant therapies used during the trial or within 1 month prior to screening will be recorded in the source documents and electronic case report form (eCRF), along with the main reason for their prescription/use.

4.3.2 Prohibited Therapy

Use of any medications other than the trial medication provided for this trial should be avoided from the screening period until completion of the trial. Occasional use of over-the-counter medications or prescription drugs may be allowed, except for those listed below and in section 4.1.2.

- Vaginal medications other than the PVR described in this protocol
- Estrogens or progestogens, other than those outlined in the protocol, administered by any route (oral, IM, vaginal). However, for those subjects with PCOS, a progestogen may be used to induce a progestogen-withdrawal bleeding episode to obtain FSH on cycle days 2-4 prior to suppression.
- Chronic, systemic corticosteroid
- Herbal remedies
- Aspirin
- OVIDREL (choriogonadotropin alfa injection)

- VIAGRA, CIALIS, LEVITRA
- Insulin-sensitizing agents (eg, metformin)
- Any medications the Investigator believes could adversely affect endometrial thickness, embryo transfer, or pregnancy
- Acupuncture

4.4 Withdrawal Criteria

Withdrawal from Trial

Every subject has the right to withdraw from the trial at any time for any reason, without the need to justify their decision. A subject's participation is to terminate immediately upon her request. However, the Investigator should record the reason for the subject's withdrawal, if possible.

If, at the time of discontination, a dose of the IMP has already been administered, the subject must be advised to consider follow-up safety investigations, which will include all procedures outlined for the Early Withdrawal Visit (section 6.3.8).

The subject can also be withdrawn from the trial at any time at the discretion of the Investigator; the reason should be discussed with the Sponsor prior to discontinuation. For any discontinuation, the Investigator will obtain all the required details and document the date of the premature termination and the main reason in the source documents and eCRF.

A subject who withdraws from the trial after embryo transfer will not be replaced.

Withdrawal of Consent

If the subject withdraws her consent, data collected up to withdrawal will remain in the database, but no further data will be collected. Samples and recordings obtained before withdrawal may be analyzed. This will be described in the Informed Consent Documents. The subject can request destruction of samples which would otherwise have been kept in storage.

5 TREATMENTS

5.1 Treatments Administered

5.1.1 Investigational Medicinal Product (IMP)

The IMPs in the present trial will be supplied as vaginal rings, which releases an average of 11 mg progesterone/day consistently over 7 days. The progesterone (20% w/w) is in a micronized formulation and dispersed evenly throughout the ring. Subjects will be instructed to insert the first PVR on the day after oocyte retrieval. A new PVR will be inserted every 7 days, and each PVR will remain in place a minimum of 23 hours/day. Depending on the subject's pregnancy assessments, PVR treatment can be continued through Week 12 of pregnancy (10 weeks post-oocyte retrieval).

For information on warnings, precautions and treatment of overdose, please refer to the Investigator's Brochure for PVR (Progesterone (FE 999913) Vaginal Ring, Investigator's Brochure).

5.1.2 Non-Investigational Medicinal Product (NIMP)

The non-investigational medicinal products (NIMPs) to be used are listed in Table 5-1.

Table 5-1 Non-investigational Medicinal Products

NIMP	Trade name	Dose
Combined oral contraceptives	CYCLAFEM 1/35 (norethindrone [1 mg] and ethinyl estradiol [0.035 mg])	1 mg/0.035 mg (1 tablet) daily for at least 14 days but no more than 21 days during the downregulation period.
GnRH agonist	LEUPROLIDE ACETATE (leuprolide acetate)	0.1 mL (500 µg)/day administered as subcutaneous injections during the downregulation period for at least 10 days but no more than 20 days, followed by 0.05 mL (250 µg/day) throughout the gonadotropin treatment period.
HP-hMG	MENOPUR (menotropin)	225 IU/day administered as subcutaneous injections for 5 days. Subsequent dosing should be adjusted according to individual subject response. Dose adjustments should not be made more frequently than once every two days and should not exceed 150 IU per adjustment. The maximum daily dose of MENOPUR should not exceed 450 IU and the minimum daily dose should not be lower than 75 IU. MENOPUR dosing should not continue for >20 days and coasting is not allowed.
hCG	NOVAREL (chorionic gonadotropin)	1 mL (2 x 5,000 IU) administered by intramuscular injection according to label as soon as 2 follicles of ≥17 mm are observed on transvaginal ultrasound.

All NIMPs are to be used in line with the recommendations in the respective products' labelling for the indication ART and/or standard clinical practice supported by literature.

For information on warnings, precautions and treatment of overdose, please refer to FDA approved Prescribing Information for CYCLAFEM 1/35, LEUPROLIDE ACETATE, MENOPUR, and NOVAREL.

5.2 Characteristics and Source of Supply

All medicinal products are provided by Ferring and will be handled according to the principles of Good Manufacturing Practice (GMP). Table 5-2 provides an overview of the presentation of each medicinal product.

Table 5-2 Characteristics of Medicinal Products

IMP / NIMP	Presentation
PVR (progesterone) Ferring Pharmaceuticals	PVR (progesterone) is provided as vaginal rings. Each ring releases an average of 11 mg progesterone/day consistently over 7 days.
CYCLAFEM 1/35 Qualitests Pharmaceuticals	CYCLAFEM 1/35 (norethindrone [1 mg] and ethinyl estradiol [0.035 mg]) is provided as oral tablets.
LEUPROLIDE ACETATE (GnRH agonist), Sandoz	LEUPROLIDE ACETATE (leuprolide acetate), is provided as a vial with sterile solution (14 mg/2.8 mL).
MENOPUR powder (menotrophin HP), Ferring Pharmaceuticals	MENOPUR powder is provided as vials with lyophilized powder and vials with diluent. After reconstitution, each vial delivers 75 IU of FSH activity and 75 IU of LH activity.
NOVAREL (hCG), Ferring Pharmaceuticals	NOVAREL (chorionic gonadotropin) is provided as vials with lyophilized powder and vials with diluent. After reconstitution, each vial delivers 5,000 IU chorionic gonadotropin.

5.3 Packaging and Labelling

Packaging and labeling of the medicinal products will be performed under the responsibility of the Clinical Trial Supply department at Ferring in accordance with GMP and national regulatory requirements. Details on the packaging of each medicinal product is provided in Table 5-3.

Table 5-3 Packaging of Medicinal Products

IMP / NIMP	Presentation
PVR (progesterone)	PVR is provided in pouches containing 1 vaginal ring.
CYCLAFEM 1/35 (combined oral contraceptive)	CYCLAFEM 1/35 is provided in boxes containing 3 blister packs, each with 28 tablets.
LEUPROLIDE ACETATE (GnRH agonist)	LEUPROLIDE ACETATE is provided in boxes containing a vial.
MENOPUR powder (menotrophin HP)	MENOPUR powder is provided in boxes containing five vials with powder and five vials with diluent.
NOVAREL (hCG)	NOVAREL is provided in boxes containing one vial with powder and one vial with diluent.

All NIMPs are commercially available and will be purchased centrally. No modification from the usual commercial state of the NIMPs will be made, except for trial-specific labelling.

All products (IMPs and NIMPs) will be labelled with trial-specific labels, which contain 1 self-adhesive tear-off portion to be affixed to the subject dispensing log maintained at the trial site.

5.4 Conditions for Storage and Use

The Investigator will ensure that the medicinal products will be stored in appropriate conditions in a secure location with controlled access as per the label for each drug. The storage compartment shall be monitored regularly and the temperature shall be documented. Deviations in storage temperature must be reported to Ferring as instructed in the IMP/NIMP handling guideline. The IMP/NIMP must not be used until authorization to proceed from the Sponsor is received.

Specific storage and use instructions for the IMP and all NIMPs are described in the package inserts and/or trial specific/commercial box labelling.

5.5 Blinding / Unblinding

5.5.1 Blinding

This is an open-label trial.

5.5.2 Unblinding of Individual Subject Treatment

This is an open-label trial.

5.6 Treatment Compliance

5.6.1 Dispensing and Accountability

The IMP (PVR) will only be dispensed to subjects who meet the eligibility criteria and are enrolled in the trial. The Investigator or designee will use the interactive response technology (IRT) system

to assign IMP and NIMP kits and record the dates and quantities dispensed to and returned by each subject, as well as manage the overall drug accountability for each subject. The monitor will review and verify the drug accountability of the IMPs and NIMPs during the trial. Any discrepancies will be documented.

5.6.2 Assessment of Compliance

In order to monitor compliance with IMP treatment, the subjects are to return all used and unused PVRs, with the exception of unused replacement ring, to the Investigator at each visit. Any unused replacement ring is to be returned at Visit 9. Used PVRs are to be returned in the provided bio-hazard bag. The Investigator or designee will reconcile and document the return in the IRT system along with the reason for missing rings, if applicable. Any physical damage to the ring should be noted by the subject in the PVR diary and collected in the eCRF. Any discrepancies should be recorded and discussed with the subject at the time of the return. Used rings are to be stored at the trial site until drug accountability has been performed by the trial monitor.

5.7 Auxiliary Supplies

Ferring will provide the sites with sanitary napkins to be used by subjects for any vaginal bleeding occurring during the trial.

5.8 Return and Destruction of Medicinal Products

The Monitor will check the supplies, the drug accountability, and inventory records at the trial site. Following this check, the Investigator will sign off on the records.

Used IMP/NIMP can be destroyed at the trial site after the drug accountability has been finalized and signed off by the Investigator, and the Sponsor has issued a written approval. Any destruction document must clearly identify the trial code and kit numbers involved, and the quantities of IMP/NIMP destroyed, including treatment visits, if applicable.

Any unused IMP/NIMP will be returned for destruction, as instructed by the Clinical Trial Supply department, Ferring Pharmaceuticals, and in accordance with local requirements, after the drug accountability has been finalized, verified by the monitor, signed off by the Investigator, and approved by the Sponsor. All unused medicinal products will be accounted for and must be destructed in a certified way.

6 TRIAL PROCEDURES

The schedule of assessments is presented in Table 6-1.

Table 6-1 Trial Schedule

Visit:	Screen (0)[a]	Down-reg.	1	2	3 OR	4	5 ET		6	6P	7		7P		8				9	End-of-trial 10
Oocyte Retrieval + X Weeks:				-2 days	0	+1 day	+5 days	1	2	2+3-4 days	3	4	4+3-4 days	5	6	7	8	9	10	12
X Weeks of Pregnancy + X days [b]:					2			3	4	4+3-4	5	6	6+3-4	7	8	9	10	11	12	14
Written informed consent	X																			
Inclusion/exclusion criteria	X																			
Demographics	X																			
Medical/gynecological history	X																			
Physical examination	X																		X	X
Pelvic examination	X					X							X		X				X	X
Height[c], weight and BMI	X																		X	X
Vital signs	X				X	X	X		X		X				X				X	X
Suppression treatment		X																		
Stimulation treatment[d]			Start	Stop																
Ovulation induction (human chorionic gonadotropin)				X																
Oocyte retrieval (OR)					X															
Embryo transfer (ET)							X													
Bleeding log (subject assessment of vaginal bleeding and blood loss)[e]						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vaginal hemorrhage assessment						X	X		X	X	X		X		X				X	X
Concomitant medications	X		X	X	X	X	X		X	X	X		X		X				X	X
Adverse events	X		X	X	X	X	X		X	X	X		X		X				X	X
LABORATORY/DIAGNOSTIC TESTS																				
Pap smear[f]	X																			
Chemistry and hematology panel	X					X[g]													X	X
Gonorrhea/chlamydia testing	X																			
Urinalysis	X																		X	X
FSH and AMH serum levels	X[h]																			
Beta human chorionic gonadotropin serum levels	X								X	X	X									
Progesterone serum levels						X	X		X										X	
Estradiol serum levels	X[h]		X[i]	X[i]		X	X													
Transvaginal ultrasound			X	X	X		X[j]						X		X				X[j]	X[j]
Abdominal ultrasound																				
PVR TREATMENT																				
Ring placement						PVR1[k,l]		PVR2	PVR3		PVR4[m]	PVR5		PVR6	PVR7[n]	PVR8	PVR9	PVR10		
Ring removal								PVR1	PVR2		PVR3	PVR4		PVR5	PVR6	PVR7	PVR8	PVR9	PVR10	

Visit:	Screen (0)[a]	Down-reg.	1	2	3 OR	4	5 ET		6	6P	7		7P		8				9	End-of-trial 10
Oocyte Retrieval + X Weeks:				-2 days	0	+1 day	+5 days	1	2	2+3-4 days	3	4	4+3-4 days	5	6	7	8	9	10	12
X Weeks of Pregnancy + X days [b]:					2			3	4	4+3-4	5	6	6+3-4	7	8	9	10	11	12	14
PVR diary						X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Drug accountability							X		X		X				X				X	

AMH = Anti-Müllerian hormone; BMI = Body Mass Index; FSH = follicle-stimulating hormone; OR = oocyte retrieval; ET = embryo transfer; P = procedural visit; PVR = progesterone vaginal ring

a. The Screening Period may last up to 90 days from the time of signing the consent form to the start of ovarian suppression.
b. In this trial, pregnancy is defined as beginning 2 weeks prior to egg retrieval.
c. Height only measured at screening
d. Stimulation will be with MENOPUR, dosed according to the label and individualized based upon subject response at the Investigator's discretion.
e. Vaginal bleeding since the previous visit will be recorded after the start of progesterone administration until the End-of-trial visit.
f. A Pap smear done within 24 months of the Screening Visit is acceptable, provided the results are normal and a copy is obtained.
g. If Visit 4 occurs on a day where shipment to the central laboratory is not feasible, e.g. during the weekend, the subject will return to the site for blood collection on the next possible day
h. Follicle-stimulating hormone (FSH) and estradiol serum levels will be measured on Cycle Day 3 ±1 day, sampling for Anti-Müllerian hormone (AMH) serum levels must be performed prior to start of ovarian suppression.
i. Analysis by local laboratory
j. Assessment of endometrial thickness by transvaginal ultrasound at Visit 5. The ultrasounds for the embryo transfer procedure at Visit 5 and the pregnancy assessments at Visit 9 and Visit 10 can be either vaginal or abdominal. If Visit 9 is an Early Withdrawal Visit due to the subject being no longer pregnant, an ultrasound is not required.
k. Ring replacement training/confirmation training will occur.
l. PVR1, PVR2, PVR3 and PVR4 will be distributed to each subject.
m. PVR5, PVR6, PVR7 and PVR-R will be distributed to each subject.
n. PVR8, PVR9, and PVR10 will be distributed to each subject.

6.1 Screening and Ovarian Suppression (Down-regulation)

Potential participants will be scheduled to come to the clinic for the screening assessments. The screening period may last up to 90 days from the time of signing the informed consent form to the start of ovarian suppression. Trial personnel will determine subject eligibility based on the inclusion and exclusion criteria.

The following procedures / assessments must take place during the screening period:

- Signed and dated written informed consent must be obtained before any trial-related examinations
- Check the inclusion and exclusion criteria
- Demographics
- Medical and gynecological history (including gonorrhoea and chlamydia testing)
- Complete physical examination (including height, weight, and BMI calculation)
- Pelvic examination (including Pap smear if not performed in the previous 24 months prior to screening)
- Vital signs
- Blood collection for assessment of:
  - Clinical chemistry and hematology parameters
  - Endocrine parameters (β-hCG, AMH, FSH, and estradiol (*Note*: AMH sampling must be performed prior to start of ovarian suppression; FSH and estradiol serum levels will be measured on cycle day 3 ±1 day))
- Urinalysis
- Recording of use of any concomitant medication
- Recording of AEs (from time of signed informed consent)

Subjects considered eligible for the trial may proceed with the following procedures / assessments:

- Start ovarian suppression with combined oral contraceptives (≥14 days to ≤21 days based on the site standard of care)
- Start leuprolide acetate at a dose of 0.1 mL (500 µg)/day 4 days prior to the last birth control pill (≥10 days to ≤20 days).

6.2 Ovarian Stimulation and Oocyte Retrieval

6.2.1 Visit 1: Start of Ovarian Stimulation

After suppression, subjects will attend the start of ovarian stimulation visit (Visit 1). Ovarian stimulation will begin on the second or third day after the start of menses in the subsequent cycle.

The following must take place at the visit:

- TVUS of ovaries (number and size of follicles)
- Blood collection for local laboratory assessment of:
  - Endocrine parameters (estradiol)
- Reduction of leuprolide acetate dose to 0.05 mL (250 µg/day)
- Start ovarian stimulation protocol with MENOPUR.
  MENOPUR will be at an initial dose of 225 IU/day for 5 days according to label. Subsequent dosing should be adjusted according to individual subject response. Dose adjustments should not be made more frequently than once every two days and should not exceed 150 IU per adjustment. The maximum daily dose of MENOPUR should not exceed 450 IU and the minimum daily dose should not be lower than 75 IU. MENOPUR dosing should not continue for >20 days and coasting is not allowed.
- Recording of use of any concomitant medication
- Recording of AEs

During stimulation, subjects will be monitored to determine when to trigger ovulation with hCG.

6.2.2 Visit 2: End of Ovarian Stimulation

The end-of-stimulation visit (Visit 2) takes place when the subject reaches the criterion for triggering of final follicular maturation. Subjects who do not reach the triggering criteria after 20 days of stimulation are to be discontinued from the trial.

Criterion for triggering of final follicular maturation with hCG:

- at least 2 follicles ≥17 mm (mean of 2 dimensions)

The following must take place at the visit:

- Blood collection for local laboratory assessment of:
  - Endocrine parameters (estradiol)
    If the estradiol level is ≥5000 pg/mL, the hCG trigger should not be administered and the subject should be discontinued from the trial.

- TVUS of ovaries (number and size of follicles)
- Dispensing/administration of hCG
- Recording of use of any concomitant medication
- Recording of AEs

6.2.3 Visit 3: Oocyte Retrieval

Oocyte retrieval (Visit 3) will take place approximately 35-37 hours after hCG administration.

The following must take place at the visit:

- Oocyte retrieval (performed under TVUS guidance)
- Vital signs
- Recording of use of any concomitant medication
- Recording of AEs

6.3 Treatment with PVR

6.3.1 Visit 4: Initiation of Treatment with PVR

Treatment with PVR will be initiated one day after oocyte retrieval (Visit 4).

The following must take place at the visit:

- Vital signs
- Blood collection for assessment of:
  - Clinical chemistry and hematology parameters (*Note:* if Visit 4 occurs on a day where shipment to the central laboratory is not feasible, e.g. during the weekend, the subject will return to the site for blood collection on the next possible day)
  - Endocrine parameters (progesterone and estradiol)
- Assessment of vaginal hemorrhage
- Pelvic examination (documentation of presence and grade [intensity] of any pain, irritation, abrasions, or lesions on the cervix or vagina or vaginal adhesions, see Appendix 2).
- Dispensing of IMP: the first 4 PVRs will be distributed (PVR1, PVR2, PVR3 and PVR4). Subjects will be instructed in the proper method for PVR insertion and removal (see Appendix 1). The subject will insert PVR1 while at the trial site. Subjects will be allowed to remove the

PVR for up to 1 hour/day; this includes removal for sexual intercourse, although this is not necessary.

- Provide subjects with PVR diary and instructions on how to complete the diary. Subjects will be asked to fill out the diary at home for each PVR used and bring it to each subsequent visit.
- Provide subjects with bleeding log and instructions as to how to differentiate between vaginal discharge and bleeding (to capture the frequency and intensity of any bleeding).
  Subjects will be asked to fill in the bleeding log at home and bring it to each subsequent visit.
- Provide subjects with sanitary napkins.
  Subjects will be instructed to use only sanitary napkins provided by the trial site for any bleeding that occurs during the trial.
- Recording of use of any concomitant medication
- Recording of AEs

6.3.2 Visit 5: Embryo Transfer

Embryo transfer (Visit 5) will occur 5 days after oocyte retrieval at the discretion of the Investigator.

The following must take place at the visit:

- Vital signs
- Blood collection for assessment of:
  - Endocrine parameters (progesterone and estradiol)
- Removal of PVR1 before embryo transfer and re-insertion of PVR1 after embryo transfer.
  If for any reason the PVR is not reinserted within one hour in order to accommodate transfer, this is to be documented.
- Review of PVR diary
- Recording of any vaginal bleeding noted in the subject's bleeding log since the previous visit
- Assessment of vaginal hemorrhage
- TVUS of uterus (endometrial thickness)
- Embryo transfer.
  The transfer will be guided by ultrasound (abdominal or transvaginal) and the procedure will be completed per the trial site's protocol.
- Assessment of drug accountability
- Recording of use of any concomitant medication
- Recording of AEs

- Subjects will be instructed to remove PVR1 and insert PVR2 at home, 7 days following the initial insertion of PVR1.

6.3.3 Visit 6: 2 Weeks After Oocyte Retrieval

Visit 6 will occur 2 weeks (14±2 days) after oocyte retrieval.

The following must take place at the visit:

- Vital signs
- Blood collection for assessment of:
  - Endocrine parameters (progesterone and β-hCG)
    If the subject has a negative β-hCG (<5 mIU/mL), treatment will be stopped and the subject will be withdrawn from the trial.
- Removal of PVR2 and insertion of PVR3 (for subjects with a positive β-hCG (≥5 mIU/mL))
  Insertion of PVR3 can be performed either at the trial site or at home.
- Review of PVR diary
- Assessment of drug accountability
- Recording of any vaginal bleeding noted in the subject's bleeding log since the previous visit
- Assessment of vaginal hemorrhage
- Recording of use of any concomitant medication
- Recording of AEs

6.3.4 Visit 6P: Procedural Visit

Subjects will attend a a procedural visit (Visit 6P), 3-4 days after Visit 6.

The following must take place at the visit:

- Blood collection for assessment of:
  - Endocrine parameters (β-hCG)
    If the subject has a negative β-hCG (<5 mIU/mL), treatment will be stopped and the subject will be withdrawn from the trial and the early withdrawal visit is to occur (section 6.3.8).
- Review of PVR diary
- Recording of any vaginal bleeding noted in the subject's bleeding log since the previous visit
- Assessment of vaginal hemorrhage
- Recording of use of any concomitant medication

- Recording of AEs

6.3.5 Visit 7: Week 5 of Pregnancy (3 Weeks After Oocyte Retrieval)

Subjects will attend Visit 7, 3 weeks (21±2 days) after oocyte retrieval.

The following must take place at the visit:

- Vital signs
- Blood collection for assessment of:
  - Endocrine parameters (β-hCG)
    If the subject has a negative β-hCG (<5 mIU/mL), treatment will be stopped and the subject will be withdrawn from the trial and the early withdrawal visit is to occur (section 6.3.8).
- Removal of PVR3 and insertion of PVR4 (for subjects with a positive β-hCG (≥5 mIU/mL))
  Insertion of PVR4 can be performed either at the trial site or at home.
- Review of PVR diary
- Assessment of drug accountability
- Recording of any vaginal bleeding noted in the subject's bleeding log since the previous visit
- Assessment of vaginal hemorrhage
- Recording of use of any concomitant medication
- Recording of AEs
- Dispensing of IMP: the next 3 PVRs and a replacement PVR to be used in the event of ring loss or damage (PVR5, PVR6, PVR7 and PVR-R) will be distributed.
  The subjects will remove and insert the PVRs at home. Subjects will be instructed to replace the PVR every 7 days. If the replacement PVR is used, the subject should obtain another replacement PVR from the trial site as soon as possible.

6.3.6 Visit 7P: Procedural Visit

Subjects will attend a procedural visit (Visit 7P), one week + 3-4 days after Visit 7.

The following must take place at the visit:

- TVUS to document the presence of an intrauterine gestational sac.
  In case of an ectopic pregnancy the subject will be treated according to the site's standard protocol. Treatment with PVR will be stopped and the subject will be withdrawn from the trial and the early withdrawal visit is to occur (section 6.3.8).
- Pelvic examiniation (documentation of presence and grade [intensity] of any pain, irritation, abrasions, or lesions on the cervix or vagina or vaginal adhesions).

If any lesions or abrasions are found on the cervix or vagina or vaginal adhesions are noted, another examination will be performed 2-4 days later.

- Review of PVR diary
- Recording of any vaginal bleeding noted in the subject's bleeding log since the previous visit
- Assessment of vaginal hemorrhage
- Recording of use of any concomitant medication
- Recording of AEs

6.3.7 Visit 8: Week 8 of Pregnancy (6 Weeks After Oocyte Retrieval)

Subjects will attend Visit 8, 6 weeks (42±2 days) after oocyte retrieval.

The following must take place at the visit:

- Vital signs
- TVUS to determine the presence and number of gestational sacs with/without fetal heart beat
- Pelvic examiniation (documentation of presence and grade [intensity] of any pain, irritation, abrasions, or lesions on the cervix or vagina or vaginal adhesions).
  If any lesions or abrasions are found on the cervix or vagina or vaginal adhesions are noted, another examination will be performed 2-4 days later.
- Recording of any vaginal bleeding noted in the subject's bleeding log since the previous visit
- Assessment of vaginal hemorrhage
- Removal of PVR6 and insertion of PVR7.
  Insertion of PVR7 can be performed either at the trial site or at home.
- Review of PVR diary
- Assessment of drug accountability
- Recording of use of any concomitant medication
- Recording of AEs
- Dispensing of IMP: the next 3 PVRs (PVR8, PVR9, and PVR10) will be distributed.
  will be distributed.
  The subjects will remove and insert the PVRs at home. Subjects will be instructed to replace the PVR every 7 days.

6.3.8 Visit 9: Week 12 of Pregnancy (10 Weeks After Oocyte Retrieval) / Early-withdrawal Visit

Visit 9 will occur 10 weeks (70±2 days) after oocyte retrieval. If a subject discontinues the trial prematurely an Early-withdrawal visit should be scheduled as soon as possible and within 1 week after last dose of the IMP.

The following procedures / assessments must take place at Visit 9 / the Early-withdrawal visit, irrespective of whether the subject discontinues the trial prematurely or continues:

- Vital signs
- Blood collection for assessment of:
  - Clinical chemistry and hematology parameters
  - Endocrine parameters (progesterone)
- Urinalysis
- Complete physical examination (including weight and BMI calculation)
- Pelvic examination (documentation of presence and grade [intensity] of any pain, irritation, abrasions, or lesions on the cervix or vagina or vaginal adhesions).
  If any lesions or abrasions are found on the cervix or vagina or vaginal adhesions are noted, another examination will be performed 2-4 days later.
- TVUS or abdominal ultrasound (pregnant subjects only) to determine the number of gestational sacs with/without fetal heart beat and estimate gestational age
- Recording of any vaginal bleeding noted in the subject's bleeding log since the previous visit
- Assessment of vaginal hemorrhage
- Review of PVR diary
- Assessment of drug accountability
- Recording of use of any concomitant medication
- Recording of AEs

6.4 End-of-trial

The End-of-trial visit (Visit 10) occurs 12 weeks (84±2 days) after oocyte retrieval (week 14 of pregnancy) / 2 weeks (14±2 days) after the last exposure to IMP.

The following end-of-trial procedures / assessments must take place:

- Vital signs

- Blood collection for assessment of:
  - Clinical chemistry and hematology parameters
- Urinalysis
- Complete physical examination (including weight, and BMI calculation)
- Pelvic examination (documentation of presence and grade [intensity] of any pain, irritation, abrasions, or lesions on the cervix or vagina or vaginal adhesions).
  If any lesions or abrasions are found on the cervix or vagina or vaginal adhesions are noted, another examination will be performed 2-4 days later.
- TVUS or abdominal ultrasound (pregnant subjects only) to determine the number of gestational sacs with/without fetal heart beat and estimate gestational age
- Recording of any vaginal bleeding noted in the subject's bleeding log since the previous visit
- Assessment of vaginal hemorrhage
- Recording of use of any concomitant medication
- Recording of AEs

After completion of the End-of-trial visit, subjects will be referred to their obstetricians for further care.

7 TRIAL ASSESSMENTS

7.1 Assessments Related to Primary Endpoint

7.1.1 Pregnancy Monitoring

7.1.1.1 β-hCG Test

Serum pregnancy tests will be obtained at 2 weeks, 2 weeks + 3-4 days, and 3 weeks after oocyte retrieval (i.e. at Visits 6, 6P, and 7). Subjects with a β-hCG level <5 mIU/mL will be discontinued from the trial.

7.1.1.2 Transvaginal Ultrasound

A TVUS will be performed at 4 weeks + 3-4 days after oocyte retrieval (Visit 7P) to document the presence of an intrauterine gestational sac, and at 6 weeks after oocyte retrieval (Visit 8) to determine the presence and number of gestational sacs with/without fetal heart beat. Ten weeks after oocyte retrieval (Visit 9), either a TVUS or abdominal ultrasound will be performed in pregnant subjects to determine the presence and number of gestational sacs with/without fetal heart beat and to estimate gestational age.

7.1.1.3 Ectopic and Heterotopic Pregnancies

If, at the TVUS performed 4 weeks + 3-4 days after oocyte retrieval, it is determined that the subject has an ectopic pregnancy, the subject will be treated according to the site's standard protocol and will be withdrawn from the trial.

If it is determined that the subject has a heterotopic pregnancy, the subject will be treated according to the site's standard protocol and may remain in the trial at the discretion of the Investigator.

7.1.2 Spontaneous Abortion

Spontaneous abortion is defined as two positive β-hCG tests occurring at least two days apart on or after 2 weeks post-oocyte retrieval, but followed by observation of any empty intrauterine gestational sac (blighted ovum), intrauterine gestation without a fetal heart beat, or absence of viable fetuses, as documented by ultrasound.

7.2 Assessments Related to Secondary Endpoints

7.2.1 Positive β-hCG

Positive β-hCG is defined as a positive serum β-hCG test at 2 weeks and 2 weeks + 3-4 days post-oocyte retrieval (Visit 6 and Visit 6P).

7.2.2 Clinical Pregnancy

Clinical pregnancy is defined as a TVUS showing at least 1 intrauterine gestational sac with fetal heart beat at 6 and 10 weeks post-oocyte retrieval (Visit 8 and Visit 9). For clinical pregnancies, the number of intrauterine sacs and fetal heart beats will be recorded.

7.2.3 Biochemical Abortion

Biochemical abortion is defined as a positive β-hCG test at 2 weeks and 2 weeks + 3-4 days post-oocyte retrieval, but followed by no observed gestational sac on a later TVUS, or followed by a negative β-hCG test.

7.2.4 Bleeding Log

Vaginal bleeding will be recorded in a Bleeding Log by the subject (Appendix 4). The subject will be instructed to use only sanitary napkins provided by the trial site for any bleeding/spotting that occurs during the trial; tampons are not permitted. This Bleeding Log will be given to all subjects at Visit 4 to capture the incidence (frequency and intensity) of any vaginal bleeding/spotting occurring throughout the trial i.e. until end-of-trial. For each incidence of bleeding/spotting, subjects will be instructed to record the date, time of day (AM versus PM), and the severity of the bleeding using a Pictorial Blood Loss Assessment chart (Wyatt, 2001). The grade (intensity) is scored as shown in Appendix 5. Bleeding deemed clinically significant in the opinion of the Investigator will be reported as an AE.

7.2.5 Vaginal Hemorrhage

The presence or absence of vaginal haemorrhage as defined in section 8.3.6 will be assessed by the Investigator at all visits starting at Visit 4 where the first distribution of PVR takes place.

7.2.6 Clinical Laboratory Variables

The following laboratory tests will be performed:

- Screening and Visits 4, 9, and 10 (End-of-trial): serum chemistry: non-fasting glucose, blood urea nitrogen, creatinine, potassium, sodium, chloride, calcium, aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transferase
- Screening and Visits 4, 9, and 10 (End-of-trial): hematology: red blood cell count, white blood cell count, hematocrit, hemoglobin, platelet count, and differential count
- Screening and Visits 9 and 10 (End-of-trial): urinalysis: specific gravity, ketones, pH, protein, blood, and glucose
- Screening: (prior to start of ovarian suppression): AMH
- Screening (Cycle Day 3 ±1 day): FSH
- Screening (Cycle Day 3 ±1 day) and Visits 1, 2, 4, and 5: serum estradiol
- Screening and Visits 6, 6P, and 7: β-hCG

- Visits 4, 5, 6, and 9: progesterone

The Investigator will review the laboratory results and evaluate and document whether the results are normal or abnormal and whether or not abnormal results are clinically significant. The laboratory report will be signed and dated by the Investigator. Results will be recorded in the subject's chart and eCRF.

7.2.7 Vital Signs

Blood pressure, heart rate, and temperature will be measured at screening and Visits 3, 4, 5, 6, 7, 8, 9, and 10 (End-of-trial). Blood pressure and heart rate are to be measured while the subject is seated under resting conditions. All blood pressure measurements should be made using the same arm and prior to any scheduled blood draws.

The Investigator will review the vital sign results and evaluate and document whether the results are normal or abnormal and whether or not abnormal results are clinically significant. Results will be recorded in the subject's chart and eCRF.

7.2.8 Pelvic Examination

A pelvic speculum examination will be performed at screening, Visits 4, 7P, 8, 9, and 10 to document the presence and grade (intensity) of any pain, irritation, abrasions, or lesions on the cervix or vagina, including the presence and grade (intensity) of any vaginal adhesions, using standardized criteria. An unscheduled pelvic speculum examination can be performed at the discretion of the Investigator for any visit with an AE reported by the subject for vaginal pain or irritation; the standardized criteria for establishing grade (intensity) are to be applied (Appendix 2). If any lesions or abrasions are found on the cervix or vagina or vaginal adhesions are noted, another examination will be performed 2-4 days later (each of these visits is to be documented as an unscheduled pelvic examination). Subjects will be followed until the lesions/abrasions or vaginal adhesions resolve or until the final assessment at the End-of-trial visit, whichever comes first. Vaginal adhesions observed can be surgically addressed based on the Investigator's judgement.

Any clinically significant finding will be reported as an AE (section 8). Results will be recorded in the subject's chart and eCRF.

7.2.9 Adverse Events

AEs will be recorded from the signed informed consent for participation in the trial at screening until the End-of-trial visit (Visit 10).

7.2.9.1 Adverse Events of Special Interest

Assessment of AEs of special interest is discussed in section 8.3.

7.3 Other Assessments

7.3.1 Demographics

Demographic information will be obtained during the screening period, including the following: date of birth, ethnicity (Hispanic or Latino, Not Hispanic or Latino) and race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White).

7.3.2 Medical/Gynecological History

A complete medical and gynecological history will be obtained at screening and will include a review of prior medical history; menstrual history; concurrent conditions by body system; history of alcohol and tobacco; and female reproductive status. Medical and gynecological history findings will be recorded in the subject's chart and eCRF.

In addition, subjects will undergo gonorrhoea and chlamydia testing at screening.

7.3.3 Physical Examination

A complete physical examination will be performed at screening, Visit 9, and Visit 10. Results will be recorded in the subject's chart and eCRF.

7.3.4 Height, Weight, and Body Mass Index Calculation

Height, weight, and body mass index (BMI) calculation will be performed at screening. In addition, weight and BMI will be assessed at Visit 9 and Visit 10. Results will be recorded in the subject's chart and eCRF.

7.3.5 Pelvic Examination and Pap Smear at Screening

A pelvic examination, including recording of baseline parameters in the pelvic examination page of the eCRF, will be conducted at screening to confirm the subject has no clinically significant gynecologic pathology or other conditions that could adversely affect pregnancy success.

In addition, a Pap smear will be performed at screening if not done in the previous 24 months. If done in the previous 24 months, the results must have been normal and a copy of the report must be filed in the subject's chart and recorded in the eCRF.

7.3.6 PVR Diary

A diary will be completed by the subject for each PVR used. Subjects will be instructed to record the date of insertion, date of removal, whether the PVR was inserted for at least 23 hours per day, and if the PVR was damaged at insertion or removal.

7.3.7 Number and Size of Follicles

TVUS will be performed at Visit 1 and Visit 2, before and after ovarian stimulation, to count the number of follicles and measure the size of the follicles. Data will be recorded separately for the right and left ovary.

7.3.8 Oocyte Retrieval

Oocyte retrieval will performed under TVUS guidance at Visit 3, the procedure will be completed per the trial site's protocol.

7.3.9 Endometrial Thickness

TVUS of the uterus to assess the endometrial thickness will be conducted at Visit 5 prior to or in connection with embryo transfer.

Endometrial thickness (composed of both layers of the endometrium) will be measured in the sagittal view of the uterus from the proximal and distal interfaces between the echogenic endometrium and the hypoechoic inner layer of the myometrium. Care should be taken not to include the hypoechoic subendometrial halo and to account for the presence of any fluid in the uterine cavity (not to be included in the endometrial thickness value). Endometrial thickness will be recorded in mm.

7.3.10 Embryo Transfer

Embryo transfer will be performed at Visit 5, 5 days after oocyte retrieval. Embryo transfer will be guided by TVUS or abdominal ultrasound and the procedure will be completed per the trial site's protocol. The number of embryos to transfer must be guided by the 2017 American Society for Reproductive Medicine (ASRM) and the Society for Assisted Reproductive Technology (SART) guidelines (SART/ASRM 2017): women with the expectation of one or more high-quality embryo(s) available for cryopreservation, and women with previous live birth after an IVF cycle, will have transfer of a single blastocyst. All other women will have transfer of no more than two blastocysts.

The number of embryos transferred will be recorded. Embryos not used for the embryo transfer in this trial may be frozen per the site's protocol.

7.3.11 Concomitant Medication

The use of any concomitant medication within the last 1 month prior to informed consent for participation in the trial (except medication used in previous infertility treatment cycles which will be recorded as part of the infertility history) and throughout the trial will be recorded. Recording of concomitant medication will be performed at all visits. Any changes in concomitant medications or treatments must be recorded at each visit.

8 ADVERSE EVENTS

8.1 Adverse Event Definition

An adverse event (AE) is any untoward medical occurrence in a subject participating in a clinical trial. It includes:

- Any unfavourable and unintended sign, symptom or disease temporally associated with the use of the IMP, whether or not considered to be caused by the IMP.
- AEs commonly observed and AEs anticipated based on the pharmacological effect of the IMP.
- Any laboratory abnormality, vital sign, or finding from physical or gynecological examination assessed as clinically significant by the Investigator (*Note*: pre-existing conditions diagnosed through assessments and examinations at the screening visit or during the screening period are not AEs, but are recorded as medical history).
- Accidental injuries, reasons for any change in medication (drug and/or dose), reasons for any medical, nursing or pharmacy consultation, or reasons for admission to hospital or surgical procedures.
- Overdoses and medication errors with and without clinical consequences.

All AEs will be coded by Ferring Global Pharmacovigilance using the Medical Dictionary for Regulatory Activities (MedDRA) (the version effective at trial start).

8.2 Collection and Recording of Adverse Events

8.2.1 Collection of Adverse Events

The Investigator must monitor the condition of the subject throughout the trial from the time of obtaining informed consent until the last visit (End-of-trial).

The sources of AEs cover:

- The subject's response to questions about her health (a standard non-leading question such as "How have you been feeling since your last visit?" is asked at each visit).
- Symptoms spontaneously reported by the subject.
- Investigations and examinations where the findings are assessed by the Investigator to be clinically significant changes or abnormalities.
- Other information relating to the subject's health becoming known to the Investigator (e.g., hospitalization).

8.2.2 Recording of Adverse Events

The Investigator must record all AEs in the AE Log provided in each subject's eCRF with information about:

- AE description
- Date and time of onset (time can be omitted, if not applicable)
- Intensity
- Causal relationship to IMP
- Action taken to IMP
- Other action taken
- Date and time of outcome (time can be omitted, if not applicable)
- Outcome
- Seriousness.

Each of the items in the AE Log is described in detail in the following sections.

Adverse Event

AEs should be recorded as diagnoses, if available. If not, separate signs and symptoms should be recorded. One diagnosis/symptom should be entered per record.

If a subject suffers from the same AE more than once and the subject recovers in between the events, the AEs should be recorded separately. If an AE changes in intensity, a worst-case approach should be used when recording the event, i.e., the highest intensity and the longest duration of the event.[1]

Note the following: a procedure is not an AE; the reason for conducting the procedure is. Hospitalization is not an AE; the reason for hospitalization is. Death is not an AE, but the cause of death is (an exception is sudden death of unknown cause, which is an AE).

[1] Exception: if an AE with onset before the first IMP administration (i.e., a pretreatment AE) worsens in intensity, this must be recorded as 2 separate events. The initial AE should be recorded with outcome "not recovered" and the date and time of outcome are when the intensity changed. The second AE should be recorded with date and time of onset when the intensity changed.

Date and Time of Onset

The date of onset is the date when the first sign(s) or symptom(s) were first noted. If the AE is an abnormal clinically significant laboratory test or outcome of an examination, the onset date is the date the sample was taken or the examination was performed.

Intensity

The intensity of an AE must be classified using the following 3-point scale:

Mild: Awareness of signs or symptoms, but no disruption of usual activity.

Moderate: Event sufficient to affect usual activity (disturbing).

Severe: Inability to work or perform usual activities (unacceptable).

The grading of AEs of special interest will be based on predefined criteria as discussed in section 8.3.

Causal Relationship to IMP

The possibility of whether the IMP caused the AE must be classified as one of the following:

Reasonable possibility: There is evidence or argument to suggest a causal relationship between the IMP and the AE. The AE may occur as part of the pharmacological action of the IMP or may be unpredictable in its occurrence.

Examples:

- AEs that are uncommon but are known to be strongly associated with IMP exposure.
- AEs that are not commonly associated with IMP exposure, but the event occurs in association with other factors strongly suggesting causation, such as a strong temporal association or the event recurs on rechallenge with the IMP.

No reasonable possibility: There is no reasonable evidence or argument to suggest a causal relationship between the IMP and the AE.

Examples:

- Known consequences of the underlying disease or condition under investigation.
- AEs common in the trial population, which are also anticipated to occur with some frequency during the course of the trial, regardless of IMP exposure.

Action Taken to IMP

The action taken to the IMP in response to an AE must be classified as 1 of the following:

- No change (medication schedule maintained or no action taken)
- Withdrawn
- Interrupted
- Not applicable

Other Action Taken

AEs requiring therapy must be treated with recognized standards of medical care to protect the health and well-being of the subject. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment of an emergency situation.

If medication is administered to treat the AE, this medication should be entered in the Concomitant Medication Log.

Date and Time of Outcome

The date and time (time can be deleted/omitted, if not applicable) the subject recovered or died.

Outcome

The outcome of an AE must be classified as one of the following:

- Recovered (fully recovered or the condition has returned to the level observed at initiation of trial treatment)
- Recovered with sequelae (resulted in persistent or significant disability/incapacity)
- Recovering (the event is improving)
- Not recovered
- Fatal.

8.3 Adverse Events of Special Interest

Standardized criteria will be applied to some AEs of special interest to establish intensity/grade (see Section 8.2.2) . Mapping of grade to intensity for these AEs is described below; additional details are provided in Appendix 2 and Appendix 3.

Grade 1: Mild

Grade 2: Moderate

Grade 3: Severe

Grade 4: Potentially Life-Threatening

Any finding of grade 4 will be designated as an SAE.

8.3.1 Vaginal Pain and Irritation

The criteria for the grading of AE's associated with vaginal pain and irritation is found in Appendix 3. The mapping of these grades to intensity criteria is described above (section 8.3). For clinical findings of pain and irritation during scheduled or unscheduled pelvic examinations the criteria for grading provided in Appendix 2 will be applied.

8.3.2 Vaginal or Cervical Abrasions and Lesions

Clinical findings of abrasions or lesions during scheduled or unscheduled pelvic examinations will be graded according to the criteria in Appendix 2. The mapping of these grades to intensity criteria is described in section 8.3.

8.3.3 Vaginal Adhesions

Clinical findings of vaginal adhesions during scheduled or unscheduled pelvic examinations will be graded according to the criteria in Appendix 2. The mapping of these grades to intensity criteria is described in section 8.3.

8.3.4 Vaginal Infection

Any occurrence of vaginal infection will be recorded as AEs.

8.3.5 Vaginal Bleeding/Spotting

Clinically significant findings of vaginal bleeding/spotting will be recorded as AEs. Collection and grading of Bleeding Log information is described in Section 7.2.4, Appendix 4 and Appendix 5.

8.3.6 Vaginal Hemorrhage

Vaginal hemorrhage is defined as a) blood loss of > 500 mL based on the opinion of the Investigator or b) hemoglobin post-treatment <10 gm/dL or c) blood loss requiring transfusion. The assessment of vaginal hemorrhage will be collected in a specific eCRF module.

8.3.7 Pregnancy Losses

Cases of biochemical abortion, spontaneous abortion, ectopic pregnancy and heterotopic pregnancy will be recorded as AEs.

8.4 Serious Adverse Events

8.4.1 Serious Adverse Event Definition

Serious adverse events (SAEs) during the trial are defined as follows:

An event is defined a SAE if it:	Guidance
results in **death**	Any event resulting in a fatal outcome must be fully documented and reported, including deaths occurring within 4 weeks after the treatment ends and irrespective of the causal relationship to the IMP. The death of a subject enrolled in a trial is *per se* not an event, but an outcome.
is **life-threatening**	The term life-threatening refers to an AE in which the subject was at immediate risk of death at the time of the event. It does not refer to an event that may have caused death if it were more severe.
requires inpatient **hospitalization** or prolongation of existing hospitalization	The term hospitalization means that the subject was admitted to hospital or that existing hospitalization was extended as a result of an event. Hospitalization describes a period of at least 24 hours. An overnight stay for observation, a stay at an emergency room, or treatment on an outpatient basis does not constitute a hospitalization. However, medical judgement must always be exercised, and when in doubt, the case should be considered serious (i.e., if case fulfills the criterion for a medically important event). Hospitalizations for administrative or social purposes do not constitute a SAE. Hospital admissions and/or surgical operations planned before trial inclusion are not considered AEs if the illness or disease existed before the subject was enrolled in the trial, provided that the condition did not deteriorate during the trial.
results in persistent or significant **disability/incapacity**	Disability/incapacity means a substantial disruption of a person's ability to conduct normal life functions. If in doubt, the decision should be left to medical judgement by the Investigator.
is a **congenital anomaly/birth defect**	Congenital anomaly/birth defect observed in any offspring of the subject conceived during treatment with the IMP.
is an **important medical event**	Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important mgedical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

8.4.2 Collection, Recording and Reporting of Serious Adverse Events

SAE Reporting by the Investigator

All SAEs must be reported **immediately** to Ferring United States Pharmacovigilance as soon as it becomes known to the Investigator and not later than within 24 hours of knowledge of the occurrence of an SAE.

The Investigator is responsible for submitting the completed SAE Report Form with the fullest possible details **within 3 calendar days** of his/her knowledge of the SAE.

SAE Report Form

The SAE Report Form is included in the eCRF system, and must be completed and submitted according to the instructions provided on the form. In case the e-CRF cannot be accessed and hence the SAE Report Form cannot be filled in within the e-CRF system, a paper SAE Report Form should be used and sent to Ferring Pharmacovigilance using the contact details below.

Ferring Pharmacovigilance
E-mail: [redacted]
US Fax: [redacted]

Completion of the Demographics, Adverse Event Log, Medical History Log and Concomitant Medication Log are mandatory for initial reports and for follow-up reports if any relevant changes have been made since the initial report. Data entries must have been made in the e-CRF for Ferring Pharmacovigilance to access the information.

Additional information relevant to the SAE such as hospital records, results from investigations, e.g., laboratory parameters (that are not already uploaded in the eCRF), invasive procedures, scans and x-rays, and autopsy results can be faxed or scanned and e-mailed to Ferring Pharmacovigilance using the contact details in the section above. In any case, this information must be supplied by the Investigator upon request from Ferring. On any copies provided, details such as subject's name, address, and hospital identification number should be concealed and instead subject number should be provided.

The Investigator will supply Ferring and the IRB with any additional requested information such as results of post-mortem examinations and hospital records.

Ferring will report SAEs according to local regulations.

8.5 Follow-up of Adverse Events and Serious Adverse Events

8.5.1 Follow-up of Adverse Events with Onset during the Trial

During the trial, from the time of obtaining informed consent until the end-of-trial visit (for each subject individually), the Investigator must follow-up on each AE until it is resolved or until the medical condition of the subject is stable.

After the subject's last trial visit, the Investigator must follow-up on any AE classified as serious or considered to have a reasonable possible causality to the IMP until it is resolved or until the medical condition of the subject is stable. All such relevant follow-up information must be reported to Ferring. If the event is a chronic condition, the Investigator and Ferring may agree that further follow-up is not required.

8.5.2 Follow-up of Adverse Events on Non-Investigational Medicinal Products During the Trial

In case an AE is recognised as an adverse drug reaction caused by a concomitant NIMP, investigators should report to each Marketing Authorisation Holder. For adverse drug reactions caused by an NIMP where Ferring is the Marketing Authorisation Holder, the case will have to be reported to Ferring.

8.5.3 Collection of Serious Adverse Events with Onset after Last Visit in the Trial

If an Investigator becomes aware of an SAE after the subject's last visit, and he/she assesses the SAE to have a reasonable possible causality to the IMP, the case will have to be reported to Ferring, regardless of how long after the end of the trial this takes place.

9 STATISTICAL METHODS

The statistical analyses will be detailed in a separate Statistical Analysis Plan.

9.1 Primary Analysis

At the final analysis, the cumulative rate of any spontaneous abortion, including spontaneous clinically recognized pregnancy loss and blighted ovum during the trial (up to Week 12 following oocyte retrieval), in subjects treated with PVR following fresh embryo transfer will be estimated (i.e., modified intention-to-treat [mITT] population).

The number and rate of any spontaneous abortions (occurring on or before 12 weeks following oocyte retrieval) for subjects in the mITT cohort will be summarized and the associated two-sided exact 95% confidence interval will be generated. Upon generating the two-sided exact 95% confidence interval, the upper bound of the interval will be assessed for whether it excludes or fails to exclude a spontaneous abortion rate of 15%.

9.2 Determination of Sample Size

In this safety trial, the primary assessment of interest is on the number of subjects that experience a spontaneous abortion. Because this is a single-arm trial, all subjects that enter the mITT analysis population will have been treated with the investigational product, PVR. The primary analysis involves the construction of a two-sided 95% exact confidence interval surrounding the proportion of subjects in the mITT analysis population that experience a spontaneous abortion. The upper bound of said confidence interval is then compared with the threshold of a 15% spontaneous abortion rate.

Statistical simulations have been performed to understand the operating characteristics under varying assumptions for both the sample size of the mITT analysis population and the “true” proportion of spontaneous abortions. For each simulation repetition, a sample of subjects was simulated using the binomial distribution and a given pair of sample size and “true” proportion of spontaneous abortions assumptions. A two-sided 95% exact confidence interval was then created based on the simulated data and the upper bound of this confidence interval was compared to the threshold of 0.15 (corresponding to a spontaneous abortion rate of 15%). If the upper bound of the two-sided 95% exact confidence interval was less than 0.15, the simulation repetition was declared a “success”. If, however, the upper bound of the two-sided 95% exact confidence interval was greater than or equal to 0.15, the simulation repetition was declared a “failure”. This process was repeated 10,000 times for each combination of assumed sample size and “true” proportion of spontaneous abortions. The proportion of simulation repetition successes to the total number of simulation repetitions then described the power of the proposed trial given the pair of assumptions.

The sample size necessary to achieve 80% power to exclude the possibility of a 15% spontaneous abortion rate after the use of PVR is described in Table 9-1. If the "true" spontaneous abortion rate is 8%, 9%, or 10%, the sample size required to achieve 80% power to exclude the possibility of a 15% spontaneous abortion rate after the use of PVR is 180, 240, or 365, respectively.

Table 9-1 Power Achieved over Varying Sample Sizes and Assumed Spontaneous Abortion Rates

Required Sample Size (mITT Analysis Population)	Assumed "True" Spontaneous Abortion Rate		
	8%	9%	10%
180	**80.3%**	64.8%	46.1%
240	93.1%	**81.8%**	63.2%
365	98.9%	94.2%	**80.9%**

mITT = modified intention-to-treat

Taking the middle of this range, a trial with 240 subjects in the mITT analysis population is considered as being adequately powered under a relevant assumption in the target population. Full simulation code is provided in Appendix 6.

9.3 Subject Disposition

The number and percentage of subjects treated with oral contraceptives, leuprolide acetate, MENOPUR, hCG, and IMP, and subjects who underwent a fresh cycle, will be summarized. Furthermore, the number of subjects that discontinue the trial during the suppression phase, stimulation phase, and after start of IMP treatment (treatment phase) will be summarized by reason for discontinuation. The subjects screened and not treated with either IMP nor NIMP (oral contraceptives, leuprolide acetate, MENOPUR, and hCG) will be presented in a separate data listing.

9.4 Protocol Deviations

Significant protocol deviations will be defined and documented prior to database lock. Details will be provided in the Statistical Analysis Plan and/or in the Clean File document.

9.5 Analysis Sets

9.5.1 mITT Cohort

The mITT cohort consists of all subjects who had successful oocyte retrieval, received at least 1 dose of IMP, and had completed fresh embryo transfer.

9.5.2 Safety Cohort

The safety cohort comprises all subjects treated with IMP.

9.5.3 Eligible Subjects (ES) Cohort

The ES cohort consists of all subjects who were deemed eligible for trial participation based on inclusion and exclusion criteria at screening and treated with oral contraceptives, leuprolide acetate, and MENOPUR.

9.6 Trial Population

9.6.1 Demographics and other Baseline Characteristics

Descriptive statistics for demographics and other baseline characteristics will be presented for the subjects in the mITT, safety, and ES cohorts.

Categorical data will be summarized using frequencies and percentages. The percentages are based on the total number of subjects within the given analysis cohort. Continuous data will be presented with the number of subjects, mean, standard deviation, median, interquartile range, minimum, and maximum. Associated demographic listings will also be produced.

9.6.2 Medical History, Concomitant Medication and Other Safety Evaluations

Medical history will be coded using the latest version of Medical Dictionary for Regulatory Activities for the mITT and ES cohorts.

9.6.3 Prior and Concomitant Medications

Prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical classification first level (alphabetically) and Anatomical Therapeutic Chemical classification second level (in decreasing order of frequency) using the latest available version of the World Health Organization Drug Dictionary. Medications will be tabulated separately for:

- Prior medication: medication taken exclusively prior to the first IMP administration (i.e., with a stop date before the date of the first IMP administration).
- Concomitant medication: medication taken after IMP administration, regardless of whether the drug began before the first IMP administration (i.e., medication that was not stopped before the date of the first IMP administration) and not started after the End-of-trial visit.

If the timing of the dose of a concomitant medication cannot be established in relation to the administration of IMP, it will be considered as a concomitant medication. Prior medication will be summarized using the mITT and ES cohorts. In contrast, concomitant medications will be analyzed using the mITT cohort.

9.7 Endpoint Assessments

9.7.1 General Considerations

Continuous variables will be described with the number of non-missing values, mean, standard deviation, median, and minimum/maximum values. Categorical variables will be described with the number and percentage of subjects within each level. All confidence intervals will be 95% confidence intervals.

9.7.2 Primary Endpoint

The primary endpoint is the cumulative rate of any spontaneous abortion occurring on or before 12 weeks following oocyte retrieval in all subjects treated with PVR and undergoing fresh embryo transfer. Spontaneous abortion is defined as two positive β-hCG tests occurring at least two days apart on or after 2 weeks post-oocyte retrieval, but followed by observation of any empty intrauterine gestational sac (blighted ovum), intrauterine gestation without a fetal heart beat, or absence of viable fetuses, as documented by ultrasound.

In addition to the analysis specified in section 9.1, the number and rates of any spontaneous abortions (occurring on or before 12 weeks following oocyte retrieval) in all subjects in the mITT cohort will be analyzed as a sensitivity analysis using a Bayesian hierarchical model to dynamically borrow information from the DR-PGN-302 study. The cumulative rate of any spontaneous abortion from Study DR-PGN-302 was 55/549 (10.2%). Dynamic borrowing between this prior data and the current trial's data allow borrowing to occur to the extent indicated by these two observed rates. More borrowing occurs when the rates are similar while less when they differ. Full modeling details are provided in Appendix 6.

9.7.3 Secondary Endpoints

9.7.3.1 Spontaneous Abortion within 6 and 10 Weeks of Oocyte Retrieval

The frequency and proportion of subjects that have any spontaneous abortion during the trial within 6 and 10 weeks post-oocyte retrieval will be derived for subjects in the mITT and safety cohorts for subjects that had ooctyte retrieved. Associated 95% confidence intervals will also be presented.

9.7.3.2 Biochemical Abortions within 6 and 10 Weeks of Oocyte Retrieval

Biochemical abortion is defined as a positive β-hCG test at 2 weeks and 2 weeks + 3-4 days post-oocyte retrieval, but followed by no observed gestational sac on a later TVUS, or followed by a negative β-hCG test. The frequency and proportion of subjects that have biochemical abortion within 6 and 10 weeks post-oocyte retrieval will be derived for subjects in the mITT and safety cohorts for subjects that had oocyte(s) retrieved. Associated 95% confidence intervals will also be presented.

9.7.3.3 Ectopic and Heterotopic Pregnancies

Ectopic and heterotopic pregnancies will be reported as AEs. The frequency and proportion of subjects with ectopic and heterotopic pregnancies will be summarized.

9.7.3.4 Positive β-hCG

Positive β-hCG is defined as a positive serum β-hCG test at 2 weeks and 2 weeks + 3-4 days post-oocyte retrieval. The positive β-hCG rate will be derived for subjects in the mITT and safety cohorts for subjects that had oocyte(s) retrieved. Associated 95% confidence intervals for these event rate estimates will also be presented.

Subjects who do not have both β-hCG tests due to missing data, early withdrawal, or any other reason will be counted as not having positive β-hCG unless a positive result is observed at a later pregnancy assessment. For example, if the outcome of these β-hCG tests is missing and a TVUS confirms clinical pregnancy at a later date then β-hCG will be imputed as 'positive'.

9.7.3.5 Clinical Pregnancy

Clinical pregnancy is defined as a TVUS showing at least 1 intrauterine gestational sac with fetal heart beat at 6 and 10 weeks post-oocyte retrieval. The frequency and proportion of subjects that are clinically pregnant at 6 and 10 weeks post-oocyte retrieval will be derived for subjects in the mITT and safety cohorts for subjects that had oocyte(s) retrieved. Associated 95% confidence intervals for these event rate estimates will also be presented.

For the clinical pregnancy rate derivation at 6 weeks post-oocyte retrieval, if a subject has missing TVUS assessment and no other TVUS assessment at a later date, the subject will be counted as not having a clinical pregnancy. In contrast, if there is a later assessment with at least 1 intrauterine gestational sac with fetal heart beat, the subject will be imputed as having a clinical pregnancy at 6 weeks post-oocyte retrieval.

9.7.4 Other Assessments

9.7.4.1 Number and Size of Follicles during Stimulation

For each subject, the number of follicles on stimulation day 1 and last day of stimulation will be summarized for the mITT and ES cohorts. The summary will include the following:

1. the number of subjects that have follicles of size <10 mm, 10 mm, 11 mm, 12 mm, 13 mm, 14 mm, 15 mm, 16 mm, and ≥17 mm,
2. a summary of the number of follicles ≥17 mm (the count for each subject will be summarized across subjects),
3. the number of subjects that have at least two folliciles that are ≥17 mm, and

4. a summary of the percentage of follicles ≥17 mm, ≥15 mm, and ≥12 mm (for each subject the percentage will be first derived and this subject level sammary will be summarized across subject using mean, SD, etc.).

9.7.4.2 E2 and Progesterone Profiles

The central laboratory E2 and progesterone profiles will be summarized for mITT and ES cohorts, using descriptive statistics by scheduled visit, as well as for the change from screening for post-screening visits.

For patients in the mITT population, the local laboratory E2 assessments will be summarized by visit.

9.7.4.3 Oocytes

For each subject, the number of oocytes retrieved, the number of germinal vesicle, metaphase I, metaphase II and Degenerated oocytes will be summarized by frequency distribution and by descriptive statistics for the mITT and ES cohorts.

9.7.4.4 Characterization of Fertilized Oocytes one Day (Day 1) after Oocyte Retrieval

The status of fertlized oocytes will be summarized 1 day after oocyte retrieval for the mITT and ES cohorts. The summary will be both at the subject level and at the oocyte level.

For the summary at the subject level, for each subject, the percentage of fertilized oocytes with pronuclei 2 pn will be derived. The percentage will be derived over the number of oocytes retrieved. These percentage will further be summarized using descriptive statastistics (i.e., mean, SD, etc.). The percentage of fertilized oocytes with continue destiny will be similarly analyzed.

For the fertlized oocyte level summary, the number and percentage of fertilized oocytes falling in each category of pronuclei will be presented (i.e., >2 pn, 2 pn, 1 pn, 0 pn and damaged). The percentage derivation will be over the total number of oocytes classified.

These summaries will be obtained for mITT and ES cohorts.

9.7.4.5 Quality of Blastocysts 5 Days (Day 5) after Oocyte Retrieval

The quality of blastocysts 5 days after oocyte retrieval will be assessed at both the blastocyst level and at the subject level. The evaluation of fertilized oocytes at Day 5 will consist of assessment of embryo stage and classification of blastocysts according to blastocyst expansion and hatching status, blastocyst inner cell mass grading and trophectoderm grading. Furthermore, the destiny of the embryo will be recorded.

Embryo stage is classified as blastocyst, morula, degenerated or cleavage stage. For embryos still at the cleavage stage the number of blastomeres will be recorded.

Destiny at Day 5 is either transferred, cryopreserved or out of trial.

The scoring of blastocysts is based on the classification system by Gardner & Schoolcraft (Gardner, 1999).

Blastocyst expansion and hatching status will be assessed as one of the following:

1. An early blastocyst, blastocoel being less than half volume of that of the embryo
2. A blastocyst with a blastocoel whose volume is half of, or greater than half of, that of the embryo
3. A blastocyst with a blastocoel completely filling the embryo
4. An expanded blastocyst with a blastocoel volume larger than that of the early embryo, with a thinning zona
5. A hatching blastocyst with the trophectoderm starting to herniate through the zona
6. A hatched blastocyst, in which the blastocyst has completely escaped from the zona

For blastocysts with expansion and hatching status on Day 5, blastocyst inner cell mass grading and trophectoderm grading will be evaluated.

Blastocyst inner cell mass grading will be assessed as one of the following:

A. Tightly packed, many cells
B. Loosely grouped, several cells
C. Very few cells

Trophectoderm grading will be assessed as one of the following:

A. Many cells forming a cohesive epithelium
B. Few cells forming a loose epithelium
C. Very few, large cells

Based on the blastocyst expansion and hatching status, blastocyst inner cell mass grading and trophectoderm grading, the embryo will be classified as a good-quality blastocyst if the grade is 3BB or above as illustrated in Table 9-2.

Table 9-2 Good-Quality Blastocysts

3AA	4AA	5AA	6AA
3AB	4AB	5AB	6AB
3AC	4AC	5AC	6AC
3BA	4BA	5BA	6BA
3BB	4BB	5BB	6BB
	4BC	5BC	6BC
	4CA	5CA	6CA
	4CB	5CB	6CB
	4CC	5CC	6CC

The embryos on Day 5 will be summarised on both the embryo level and at the subject level.

Embryo Level

At the embryo level all embryos evaluated will be included in the tables when reporting embryo stage and destiny of the embryo. For summary of blastocyst expansion and hatching status, blastocyst inner cell mass grading and trophectoderm grading all available embryo evaluations will be included. Frequency tables will be produced for the embryo stage, destiny, blastocyst expansion and hatching status, blastocyst inner cell mass grading and trophectoderm grading. These summaries will be obtained for the subjects in the mITT and ES cohorts.

Subject Level

At the subject level the following will be derived for all subjects in the mITT and ES cohorts for the subjects that had oocytes retrieved:

- Number of blastocysts at Day 5
- Number of good-quality blastocysts at Day 5

These counts will be summarized using descriptive statistics of mean, median, SD, minimum and maximum.

9.7.4.6 Endometrial Thickness

Endometrial thickness at the time of blastocyst transfer will be summarized for the mITT and ES cohorts.

9.8 Extent of Exposure and Treatment Compliance

9.8.1 PVR

The total number of PVRs used and the duration of treatment will be summarized. The total number of subjects who prematurely discontinued PVR and the associated reasons for discontinuation will also be summarized. Furthermore, the drug compliance rate will also be summarized for the mITT and safety cohorts. Compliance is defined as follows:

(number of PVRs used)/ (number of PVRs expected to be used).

These summaries will be generated for the safety cohort. Additional information collected in the drug accountability eCRF module may be summarized. A detailed associated listing will be produced.

9.8.2 Oral Contraceptives

The type of oral contraceptives used and the duration of treatment will be summarized for the ES and safety cohorts.

9.8.3 MENOPUR, Leuprolide Acetate, and hCG

The total dose of MENOPUR and leuprolide acetate administered and the duration of treatment will be summarized for the ES and safety cohorts. The number of subjects that receive hCG will also be summarized for the ES and safety cohorts.

9.9 Safety

9.9.1 General Considerations

Safety parameters will be evaluated for the ES and safety cohorts. Safety summaries will be presented by the 5 phases of the trial. These phases are defined as follows:

- Screening Phase: From the date of signing the informed consent through the day before the start of the oral contraceptive treatment.
- Suppression Phase: From the start of oral contraceptive treatment until the day before the start of the stimulation phase (start of MENOPUR treatment).
- Stimulation Phase: From the date of the first dose of MENOPUR through the day before the start of IMP.
- Treatment Phase: From the date of the first dose of IMP (PVR) through the end of the trial.
- Study Phase: From the date of the first dose of oral contraceptive through the end of the trial.

9.9.2 Adverse Events

Treatment-emergent AEs are AEs that occur during the treatment phase or a pre-existing medical condition that worsened in intensity during the treatment phase. Treatment-emergent AEs will be summarized overall and tabulated by system organ class and preferred term using the latest available Medical Dictionary for Regulatory Activities dictionary. The total number of subjects reporting at least 1 AE, the percentage of subjects with an AE, and the number of events reported will be presented.

Summary tables will be prepared for:

- All treatment-emergent AEs
- Treatment-emergent AEs by causality (related/unrelated)
- Treatment-emergent AEs leading to death
- Treatment-emergent AEs by intensity
- Treatment-emergent SAEs
- Treatment-emergent AEs leading to discontinuation
- Treatment-emergent AEs with an incidence of at least 5%
- Non-serious treatment-emergent AEs with an incidence of at least 5%

Furthermore, the overall AE summary table by system organ class and preferred term will also be produced for the study phase, suppression phase, and the stimulation phase for the ES and safety cohorts.

A separate AE listing will be provided for the screening phase, suppression phase, stimulation phase, and treatment phase of the trial.

9.9.2.1 Treatment-Emergent AEs of Special Interest

Standardized criteria will be applied to some AEs of special interest to establish intensity/grade. For AEs associated with vaginal bleeding/spotting, vaginal pain and irritation, and vaginal or cervical abrasions and lesions, standardized criteria will be used by the sites to record the intensity of these AEs (see section 8.3 and Appendix 2, Appendix 3, and Appendix 4). For these AEs and AEs associated with vaginal haemorrhage, vaginal infection and vaginal adhesions, a summary table of the treatment-emergent AEs of special interest will be produced by preferred term, grade (intensity), and seriousness for subjects in the safety cohort for the treatment phase and the study phase.

9.9.3 Safety Laboratory Variables

For each laboratory parameter (hematology, chemistry, and urinalysis), the number of subjects with abnormal laboratory values will be summarized for the study phase and the stimulation phase for the

ES and safety cohorts. This summary will also be produced for the treatment phase for the safety cohort.

9.9.4 Vital Signs

For each vital sign parameter, the number of subjects with abnormal vital signs will be summarized for the study phase and stimulation phase for the ES and safety cohorts. This summary will also be produced for the treatment phase for the safety cohort.

9.9.5 Bleeding Log

At the start of PVR, each subject will receive a bleeding log (see section 8.3 and Appendix 4). For each incidence of sanitary napkin use for bleeding/spotting, subjects will be instructed to record the date, time of day, and the severity of the bleeding. For each subject, for each day: the grade (intensity) of bleeding associated with each sanitary napkin use will be summed. The sum of the daily grades (intensity) of bleeding will be averaged by visit window where the visit window will cover the subject's Bleeding Log recording period (i.e., from the start of the PVR to the End-of-trial visit). Finally, this subject data will be summarized across all subjects for the safety cohort by visit window. The summary will include mean, median, standard deviation, minimum and maximum. Furthermore, this analysis will be repeated removing the periods associated with AEs reported as vaginal hemorrhage, the primary endpoint of spontaneous abortion, the secondary endpoint of biochemical abortion and information collected after the cessation of the use of PVR.

9.9.6 Vaginal Hemorrhage

The number of subjects with vaginal hemorrhage (see Sections 7.2.5 and 8.3.6) will be summarized for the safety cohort.

9.9.7 Pelvic Examination

A pelvic examination will be performed at screening, Visits 4, 7P, 8, 9, and 10 to document the presence and grade (intensity) of any pain, irritation, abrasions, or lesions on the cervix or vagina using standardized criteria, and the presence and grade (intensity) of any vaginal adhesions using standardized criteria (Appendix 2). If any lesions or abrasions are found on the cervix or vagina or vaginal adhesions are noted, another examination will be performed 2-4 days later. The grade (intensity) for each type of assessment will be summarized by visit for the safety cohort. Furthermore, a shift table will be presented summarizing the change in grade (intensity) from Visit 4 to the End-of-trial, where the End-of-trial is defined to be the last assessment in the treatment phase.

An associated listing will also be produced.

9.10 Interim Analyses

No interim analysis is planned.

10 DATA HANDLING

10.1 Source Data and Source Documents

Source Data – International Council for Harmonisation (ICH) Definition

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source Documents - ICH Definition

Source documents are defined as original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).

Trial-specific Source Data Requirements – Ferring

Source documents need to be preserved for the maximum period of time permitted by local requirements. For each subject enrolled, the Investigator will indicate in the source documents that the subject participates in this trial, and will record at least the following information, if applicable:

- Existence of subject (initials, date of birth)
- Confirmation of participation in trial (trial ID, subject ID)
- Informed consent (date and time of oral information, date and time of handing out Informed Consent Documents, date and time of obtaining written informed consent)
- Eligibility for participation in the trial (documenting all inclusion / exclusion criteria)
- Relevant medical and gynecological history
- Visit dates
- Dates of administration of IMP
- Dates and doses of NIMP
- Dates and doses of concomitant medication
- Results of β-hCG tests and TVUS at Visits 6, 6P, 7, 8, 9 and 10
- Adverse events (description as well as start/stop date and time)

- Reason for discontinuation

The source data for analytical parameters of blood samples will be available at the central laboratory. The source data for vaginal bleeding/spotting will be the subject´s bleeding log. The source data for dates of insertion and removal of each PVR will be the subject´s PVR diary.

No specific protocol data can be recorded directly in the e-CRF without prior written or electronic record.

10.2 eCRF/Case Report Form

An eCRF system provided by an independent third-party contract research organization (CRO) will be used for data capture. The system is validated and access at all levels to the system is granted/revoked following Ferring and vendor procedures, in accordance with regulatory and system requirements.

Trial data should be entered into the eCRF in a timely manner. The time-frame will be specified in the investigator agreement as well as in the eCRF guideline.

The Investigator will approve/authorize the eCRF entries for each subject with an electronic signature that is equivalent to a handwritten signature.

The eCRF system and the database will be hosted at the independent third-party CRO. After the trial database is declared clean and released to the statistician, a final copy of the database will be stored at Ferring. The Investigator will also receive a copy of the trial site's final and locked data (including audit trail, electronic signature, and queries) as write-protected PDF files produced by the independent third-party CRO. The PDF files will be stored in an electronic format and will be provided to the Investigator before access to the eCRF is revoked.

Entry errors occurring in the eCRF will be corrected electronically. Such corrections or modifications will be automatically tracked by an audit trail detailing the date and time of the correction and the name of the person making the correction.

10.3 Data Management

A data management plan will be created under the responsibility of the Global Biometrics Department, Ferring. The data management plan will be issued before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning, and validation.

The data management plan will also include information about the intended use of computerised systems, a description of the security measures employed to protect the data and a description of the electronic data flow.

10.4 Provision of Additional Information

On request, the Investigator will provide Ferring with additional data relating to the trial, duly anonymized and protected in accordance with applicable requirements.

11 MONITORING PROCEDURES

11.1 Periodic Monitoring

The monitor will contact and visit the Investigator periodically to ensure adherence to the protocol, ICH-Good Clinical Practice (GCP), standard operating procedures and applicable regulatory requirements, maintenance of trial-related source records, completeness, accuracy, and verifiability of eCRF entries compared to source data, verification of drug accountability, and compliance with safety reporting instructions.

The Investigator will permit the monitor direct access to all source data, including electronic medical records, and/or documents in order to facilitate data verification. The Investigator will cooperate with the monitor to ensure that any discrepancies that may be identified are resolved. The Investigator is expected to be able to meet the monitor during these visits. When the first subject is enrolled at the trial site, a monitoring visit will take place shortly afterwards. For this trial, the frequency of the monitoring visits per site will be determined by the enrolment rate.

The source data verification process and definition of key variables to be monitored and the monitoring strategy will be described in detail in the Monitoring Plan for the trial.

11.2 Audit and Inspection

The Investigator will make all the trial-related source data and records available at any time to quality-assurance auditor(s) mandated by Ferring, or to domestic/foreign regulatory inspectors or representatives from IRBs who may audit/inspect the trial.

The main purposes of an audit or inspection are to assess compliance with the trial protocol and the principles of ICH-GCP, including the Declaration of Helsinki and all other relevant regulations.

The subjects must be informed by the Investigator and in the informed consent documents that authorized Ferring representatives and representatives from regulatory authorities and IRBs may wish to inspect their medical records. During audits/inspections, the auditors/inspectors may copy relevant parts of the medical records. No personal identification, apart from the screening number, will appear on these copies.

The Investigator should notify Ferring without any delay of any inspection by a regulatory authority or IRB.

11.3 Confidentiality of Subject Data

The Investigator will ensure that the confidentiality of the subjects' data will be preserved. In the eCRF or any other documents submitted to Ferring, the subjects will not be identified by their names, but by an identification system, which consists of an assigned number in the trial. Documents that are not for

submission to Ferring, e.g., the confidential subject identification code and the signed informed consent documents, will be maintained by the Investigator in strict confidence.

12 CHANGES IN THE CONDUCT OF THE TRIAL

12.1 Protocol Amendments

Any change to this protocol will be documented in a protocol amendment issued by Ferring, and agreed upon by the Investigator and Ferring prior to its implementation. Amendments may be submitted for consideration to the approving IRBs and regulatory authorities, in accordance with local regulations. Changes to the protocol to eliminate immediate hazard(s) to trial subjects may be implemented prior to IRB approval or favourable opinion.

12.2 Deviations from the Protocol

Deviations from the protocol should not occur. If deviations from the protocol occur, the Investigator must inform the monitor, and the implications of the deviation must be reviewed and discussed. Any deviation must be documented, either as an answer to a query in the eCRF, in a protocol deviation report in the eCRF, or a combination of both. A log of significant protocol deviation reports will be maintained by Ferring. Protocol deviation reports and supporting documentation must be kept in the Investigator's File and in the trial master file.

12.3 Premature Trial Termination

Both the Investigator (with regard to his/her participation) and Ferring reserve the right to terminate the trial at any time. Should this become necessary, the procedures will be agreed upon after consultation between the two parties. In terminating the trial, Ferring and the Investigator will ensure that adequate consideration is given to the protection of the best interests of the subjects. Regulatory authorities and IRBs will be informed.

In addition, Ferring reserves the right to terminate the participation of individual trial sites. Conditions that may warrant termination include, but are not limited to, insufficient adherence to protocol requirements and failure to enter subjects at an acceptable rate.

13 REPORTING AND PUBLICATION

13.1 Clinical Trial Report

The data and information collected during this trial will be reported in a clinical trial report prepared by Ferring and submitted for comments and signature to the signatory Investigator.

13.2 Confidentiality and Ownership of Trial Data

Any confidential information relating to the IMP or the trial, including any data and results from the trial, will be the exclusive property of Ferring. The Investigator and any other persons involved in the trial will protect the confidentiality of this proprietary information belonging to Ferring.

13.3 Publications and Public Disclosure

13.3.1 Publication Policy

At the end of the trial, one or more manuscripts for joint publication may be prepared in collaboration between the Investigator(s) offered authorship and Ferring. In a multisite trial based on the collaboration of many sites, any publication of results must acknowledge all sites. Results from multisite trials must be reported in entirety in a responsible and coherent manner and results from subsets should not be published in advance or without clear reference to the primary publication of the entire trial.

Authorship is granted based on the International Committee of Medical Journal Editors criteria (see current official version: http/www.ICMJE.org). The total number of authors is based on the guideline from the relevant journal or congress. In the event of any disagreement in the content of a publication, both the Investigator's and Ferring's opinion will be fairly and sufficiently represented in the publication.

Any external CRO or laboratory involved in the conduct of this trial has no publication rights regarding this trial.

If the Investigator wishes to independently publish/present any results from the trial, the draft manuscript/presentation must be submitted in writing to Ferring for comment prior to submission. Comments will be given within 4 weeks from receipt of the draft manuscript. This statement does not give Ferring any editorial rights over the content of a publication, other than to restrict the disclosure of Ferring's intellectual property. If the matter considered for publication is deemed patentable by Ferring, scientific publication will not be allowed until after a filed patent application is published. Under such conditions, the publication will be modified or delayed at the Investigator's discretion, to allow sufficient time for Ferring to seek patent protection of the invention.

13.3.2 Public Disclosure Policy

ICMJE member journals have adopted a trial-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public clinical trials registry. Thus, it is the responsibility of Ferring to register the trial in an appropriate registry, i.e., www.ClinicalTrials.gov, a website maintained by the National Library of Medicine at the United States National Institutes of Health. Trial registration may occur in other registries in accordance with local regulatory requirements. A summary of the trial results is made publicly available in accordance with applicable regulatory requirements.

14 ETHICAL AND REGULATORY ASPECTS

14.1 Institutional Review Board

An IRB will review the protocol and any amendments and advertisements used for recruitment. The IRB will review the subject information sheet and the informed consent form, their updates (if any), and any written materials given to the subjects. A list of all IRBs to which the protocol has been submitted and the name of the committee chairmen will be included in the clinical trial report.

14.2 Regulatory Authority Authorization/Approval/Notification

The regulatory permission to perform the trial will be obtained in accordance with applicable regulatory requirements. All ethical and regulatory approvals must be available before a subject is exposed to any trial-related procedure, including screening tests for eligibility.

14.3 End-of-Trial and End-of-Trial Notification

The end of the trial is defined as the date of LPLV, i.e. when the last subject completes the end-of-trial visit. The IRBs and relevant regulatory authorities will be notified about the completion of the clinical trial according to local legislation.

In the case of early termination for safety reasons, Ferring must notify the end of the trial to the relevant regulatory authorities and the concerned IRBs without delay, clearly explain the reasons, and describe follow-up measures, if any.

Within one year of the end of the trial, Ferring shall send the final clinical trial report to the relevant regulatory authorities.

14.4 Ethical Conduct of the Trial

This trial will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, in compliance with the approved protocol, ICH-GCP, and applicable regulatory requirements.

14.5 Subject Information and Consent

The Investigator (or the person delegated by the Investigator) will obtain a freely given written consent from each subject after an appropriate explanation of the aims, methods, sources of funding, any possible conflicts of interest, anticipated benefits, potential risks of the trial and the discomfort it may entail, post-trial provisions, and any other aspects of the trial that are relevant to the subject's decision to participate. The trial subject must be given ample time to consider participation in the trial, before the consent is obtained. The informed consent documents must be signed and dated by the subject and the Investigator, or the person delegated by the Investigator, who has provided information to the subject regarding the trial before the subject is exposed to any trial-related procedure, including

screening tests for eligibility. Subjects must be given the option of being informed about the general outcome and the results of the trial.

The Investigator (or the person delegated by the Investigator) will explain that the subject is completely free to refuse to enter the trial or to withdraw from it at any time, without any consequences for her further care and without the need to justify her decision.

The subject will receive a copy of the subject information and her signed informed consent form.

If new information becomes available that may be relevant to the trial subject's willingness to continue participation in the trial, a new subject information and informed consent form will be forwarded to the IRBs (and regulatory authorities, if required). The trial subjects will be informed about this new information and re-consent will be obtained.

Each subject will be informed that the monitor(s), quality-assurance auditor(s) mandated by Ferring, IRB representatives, or regulatory authority inspector(s), in accordance with applicable regulatory requirements, may review her source records and data. Data protection will be handled in compliance with national/local regulations.

14.6 Subject Participation Card

Each subject will be provided with a subject participation card bearing the following information:

- That she is participating in a clinical trial (including trial code)
- That she is being treated with PVR
- The name and phone number of the Investigator
- The name, address and phone number of a Ferring contact

The subject will be asked to keep the subject participation card in her possession at all times during the trial and to return it at the last trial visit, if applicable.

Each subject's primary care physician will be notified of her participation in the trial by the Investigator, if the subject agrees and if applicable.

14.7 Compliance Reference Documents

The Declaration of Helsinki, the consolidated ICH-GCP, and other national law(s) in the country(ies) where the trial takes place shall constitute the main reference guidelines for ethical and regulatory conduct.

15 LIABILITIES AND INSURANCE

15.1 ICH-GCP Responsibilities

The responsibilities of Ferring, the monitor, and the Investigator will be defined in the ICH-GCP consolidated guideline, and applicable United States regulatory requirements. The Investigator is responsible for adhering to the ICH-GCP responsibilities of Investigators, for dispensing and reconciliation of the IMP in accordance with the approved protocol or an approved amendment, and for its secure storage and safe handling throughout the trial.

15.2 Liabilities and Insurance

Ferring is, as Sponsor, responsible for ensuring appropriate general/product liability insurance and, as required in accordance with applicable laws and regulations, United States-specific liability insurance coverage for claims made by a trial subject for injury arising from the subject's participation in the trial.

16 ARCHIVING

16.1 Investigator File

The Investigator is responsible for maintaining all the records, which enable the conduct of the trial at the site to be fully understood, in compliance with ICH-GCP. The trial documentation including all the relevant correspondence should be kept by the Investigator for at least 15 years after the completion or discontinuation of the trial, if no further instructions are given by Ferring.

The Investigator is responsible for the completion and maintenance of the confidential subject identification code, which provides the sole link between named subject source records and anonymous eCRF data for Ferring. The Investigator must arrange for the retention of this subject identification log and signed informed consent documents for at least 15 years after the completion or discontinuation of the trial.

No trial site document may be destroyed without prior written agreement between the Investigator and Ferring. Should the Investigator elect to assign the trial documents to another party, or move them to another location, Ferring must be notified. If the Investigator retires and the documents can no longer be archived by the site, Ferring can arrange having the Investigator file archived at an external archive.

16.2 Trial Master File

Ferring will archive the Trial Master File in accordance with ICH-GCP and applicable regulatory requirements.

17 REFERENCES

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Practice Committee of the Society for Assisted Reproductive Technology and Practice Committee of the American Society for Reproductive Medicine. Guidance on the limits to the number of embryos to transfer: a committee opinion. Fertil Steril 2017; 107:901–3.

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APPENDICES

Appendix 1 Sample Subject Instructions For Use

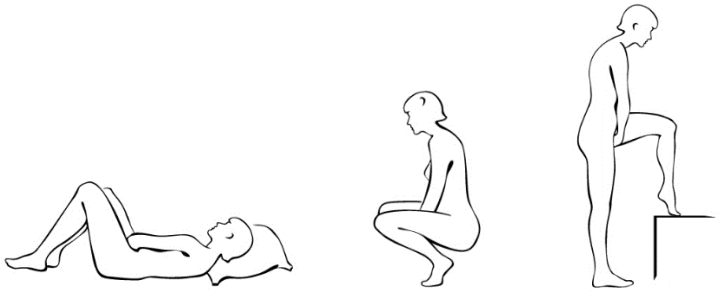
How should I use Progesterone Vaginal Ring?

Use progesterone vaginal ring (PVR) exactly as prescribed. The usual dose of PVR is one ring placed in your vagina and replaced weekly for up to a total of 10 weeks, unless your Doctor/Investigator advises otherwise.

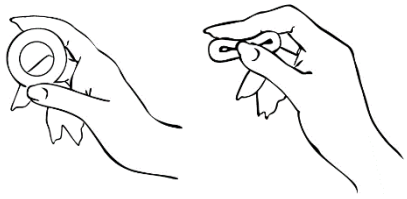
Follow the steps below:

Save foil pouch, bio-hazard plastic bag, and outer carton for later use to return the used ring at your next visit.

1. After washing your hands, remove the vaginal ring from its foil pouch.
2. Choose the position that is most comfortable for you (for example: lying down, squatting, or standing with one leg up).

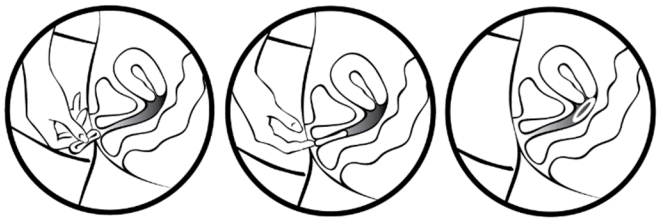


3. To insert the ring, hold the ring between your thumb and index finger and gently squeeze the opposite sides of the ring together.



4. Use your other hand and hold open the folds of skin around your vagina.

5. Place the tip of the ring in the vaginal opening and then use your index finder to push the folded ring gently into your vagina. Push it up towards your lower back as far as you can. If you can feel the ring, it may not be placed back far enough in your vagina. Use your index finder to push it back a bit further. There is no danger of the vaginal ring being pushed too far up in the vagina or getting lost.

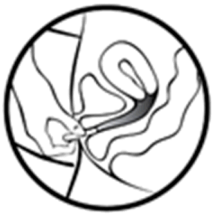


This is all you need to do to place the ring in the correct position. The ring will conform to fit your body. The exact position is not important, as the muscles of your vagina should keep the ring securely in place. Put the ring where it is comfortable for you. If you have difficulty inserting the ring, it is fine to rinse it with cool to lukewarm (not hot) water before insertion.

To remove:

1. Wash your hands.
2. Choose the position that is the most comfortable for you.
3. Put a finger into your vagina and hook it through the ring.

4. Gently pull downwards and forward to remove the ring.



5. Place the used ring in the foil pouch and place the foil pouch in the bio-hazard plastic bag (supplied in the carton with the study materials) and seal the bag.

6. Place the **sealed** bio-hazard bag in the original outer carton and return to the doctor/investigator or study personnel at your next visit

7. Keep out of reach of children and pets.

Other Information for Using Progesterone Vaginal Ring

- If the vaginal ring is expelled, it should be rinsed with cool to lukewarm (not hot) water and reinserted as soon as possible, except if fecally-contaminated. If fecally-contaminated, the vaginal ring should be replaced.

- The vaginal ring should remain in place for a minimum of 23 hours per day. It may be removed for sexual intercourse, although this is not necessary.

- If you forgot to remove the vaginal ring at the scheduled time, replace the used ring with a new ring as soon as possible.

- Do not insert more than one progesterone vaginal ring at a time.

- Do not use any other vaginal products when you are using progesterone vaginal ring.

- This leaflet summarizes the most important information about the use of the progesterone vaginal ring. If you would like more safety information, talk with your Doctor/Investigator or Study personnel.

Appendix 2 Pelvic Examination, Grade, and Criteria

PARAMETER	INDIVIDUAL SIGNS/SYMPTOMS				
	GRADE 0 NORMAL	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Pain	None	Pain causing no or minimal inference with usual social & functional activities	Pain causing greater than minimal inference with usual social & functional activities or the need for non-narcotic medication	Pain causing inability to perform usual social & functional activities or the need for narcotic medication	Disabling pain causing inability to perform basic self-care functions OR hospitalization (other than emergency room visit) indicated
Dyspareunia (pain with sexual activity)	None	Pain causing no or minimal inference with sexual function	Pain causing greater than minimal inference with sexual function	NA	NA
Tenderness* (Specify Area: Vulvar/Perineum, Vagina, Cervix (including cervical motion tenderness), Uterus, Adnexae, Pelvic/Lower Abdominal, or Ovulatory)	None	Mild tenderness	Moderate tenderness	Severe tenderness	NA
	GENITOURINARY IRRITATION - VULVA				
Vulvar/vaginal itching	None	Itching causing no, mild or moderate inference with usual social & functional activities	Itching causing inability to perform usual social & functional activities; may require intervention such as antihistamine or bathing to provide relief	NA	NA
Vulvar edema	None	Mild, non-pitting edema	Moderate, 1-2+ pitting edema	3+ pitting edema, severe enough to require urinary drainage, or weeping edema ± skin breakdown	NA

PARAMETER	INDIVIDUAL SIGNS/SYMPTOMS				
	GRADE 0 NORMAL	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Vulvar erythema	None	Erythema covering <50% of vulvar surface	Erythema covering >50% of vulvar surface	NA	NA
Vulvar rash	None	Rash covering <50% of vulvar surface	Rash covering >50% of vulvar surface	Severe epithelial disruption with hospitalization indicated	NA
Bartholin's or Skene's gland	No findings	Cyst with no inflammation	Cyst or abscess with outpatient intervention indicated	Cyst or abscess with hospitalization indicated	Necrotizing fasciitis from Bartholin's abscess
GENITOURINARY LESIONS - VULVA					
Vulvar lesions (findings seen only by colposcopy should not be included here)	Normal variants including skin tags, moles, scars, etc.	Blisters, ulcerations, or pustules – no treatment indicated	Blisters, ulcerations, or pustules, with treatment indicated	Severe epithelial disruption with hospitalization indicated	NA
GENITOURINARY IRRITATION – VAGINA					
Vaginal edema	None	Mild-moderate engorgement	Loss of ruggae and friability	NA	NA
Vaginal erythema	None	Erythema <50% of vaginal surface	Erythema >50% of vaginal surface	NA	NA
Vaginal dryness	No complaint	Dryness causing no or minimal inference with usual sexual, social & functional activities	Dryness causing greater than minimal inference with usual sexual, social & functional activities	NA	NA
Vaginal discharge by participant report	Participant's usual amount of discharge, regardless of color or quantity	Mild-moderate increase in amount above participant baseline – no sanitary protection required	Profuse increase in discharge requiring pad use or other hygienic intervention	NA	NA
Vaginal discharge as observed by clinician	Slight amount of discharge, any color	Mild-moderate increase in amount	Significant increase in amount with pooling in vagina on examination	NA	NA

PARAMETER	INDIVIDUAL SIGNS/SYMPTOMS				
	GRADE 0 NORMAL	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
GENITOURINARY LESIONS, ABRASIONS– VAGINA					
Vaginal abrasions or laceration (including probable applicator injuries)	None	Superficial disruptions and disruptions extending through the mucosa with minimal impact on life	Large disruptions extending through the mucosa or large superficial disruptions, hospitalization not indicated	Large disruptions extending through the mucosa or large superficial disruptions, hospitalization indicated	NA
Vaginal lesions (findings seen only by colposcopy should not be included here)	Normal variants including skin tags, moles, scars, etc.	Blisters, ulcerations, or pustules, no treatment indicated	Blisters, ulcerations, or pustules with treatment indicated	Severe epithelial disruption requiring hospitalization	NA
GENITOURINARY IRRITATION – CERVIX					
Cervical edema and friability	None	Edema without friability	Friable cervix	NA	NA
Cervical erythema	None	Erythema covering <50% of cervix	Erythema covering >50% of cervix	NA	NA
Cervical discharge	White or clear discharge	Small amount of purulent discharge at os	Purulent discharge extending onto cervix or vagina	NA	NA
GENITOURINARY LESIONS – CERVIX					
Visible cervical lesions (findings seen only by colposcopy should not be included here)	Normal variants including skin tags, moles, scars, etc.	Blisters, ulcerations, or pustules, no treatment indicated	Blisters, ulcerations, or pustules with treatment indicated	NA	NA
VAGINAL ADHESIONS – VAGINA					
Vaginal Adhesion	None	Asympotomatic, manual removal of ring possible	Symptomatic (eg. irritation reported by patient), manual removal of ring possible	Surgical intervention (eg. adhesiolysis) required to resolve	Potentially life threatening; urgent intervention indicated.

***** If both pain and tenderness are present, only report the one with the most severe grade

Note: Any finding deemed clinically significant after initiation of treatment is to be reported as an AE.

Adapted from: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Addendum 1 (Female Genital Grading Table for Use In Microbicide Studies); November 2007.

Appendix 3 Assessment of AEs of Special Interest: Vaginal Pain and Vaginal Irritation

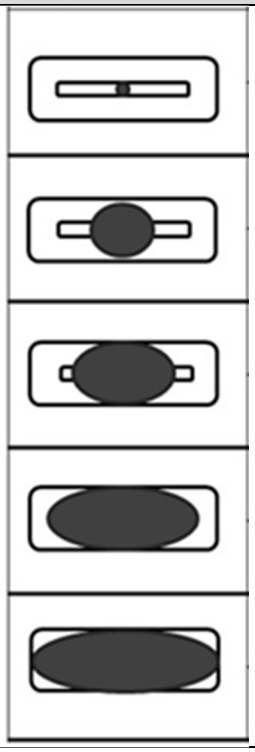
INDIVIDUAL SIGNS/SYMPTOMS				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
VAGINAL PAIN				
Pain	Pain causing no or minimal inference with usual social & functional activities	Pain causing greater than minimal inference with usual social & functional activities or the need for non-narcotic medication	Pain causing inability to perform usual social & functional activities or the need for narcotic medication	Disabling pain causing inability to perform basic self-care functions OR hospitalization (other than emergency room visit) indicated
Dyspareunia (pain with sexual activity)	Pain causing no or minimal inference with sexual function	Pain causing greater than minimal inference with sexual function	NA	NA
VAGINAL IRRITATION				
Vaginal itching	Itching causing no, mild or moderate inference with usual social & functional activities	Itching causing inability to perform usual social & functional activities; may require intervention such as antihistamine or bathing to provide relief	NA	NA
Vaginal dryness	Dryness causing no or minimal inference with usual sexual, social & functional activities	Dryness causing greater than minimal inference with usual sexual, social & functional activities	NA	NA
Vaginal discharge by participant report	Mild-moderate increase in amount above participant baseline – no sanitary protection required	Profuse increase in discharge requiring pad use or other hygienic intervention	NA	NA

Adapted from: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Addendum 1 (Female Genital Grading Table for Use In Microbicide Studies); November 2007.

Appendix 4 Bleeding Log

Bleeding Log

Please record each use of a sanitary napkin related to vaginal bleeding. Tampons cannot be used.

Date	Time of Day	Sanitary Napkin
□□ □□□ 2 0 1 □ d d m m m y y y y	□□:□□ AM □ h h m m PM □	

Adapted from: Wyatt KM, Dimmock PW, Walker TJ, O'Brien PM. Determination of total menstrual blood loss. Fertil Steril. 2001;76(1):125-31.

Appendix 5 Scoring of Bleeding Log Information

Napkin	Grade
	1
	2
	3
	4
	5

Adapted from: Wyatt KM, Dimmock PW, Walker TJ, O'Brien PM. Determination of total menstrual blood loss. Fertil Steril. 2001;76(1):125-31.

Appendix 6 Primary Analysis Simulation Code and the Sensitivity Analysis Operating Characteristics

Primary Analysis Simulation Code

Below is the R code that runs the simulation described in the sample size justification.

```
##################
### LIBRARIES ###
##################

library(ggplot2)
library(tidyverse)

#############
### SETUP ###
#############

### SET THE SEED ###
set.seed(7639216)

### THE NUMBER OF SIMULATION REPS ###
n.sim <- 10000

### THE NUMBER OF SUBJECTS IN THE MODIFIED ITT ANALYSIS POPULATION ###
n.mitt <- seq(from = 100, to = 400, by = 5)

### THE TRUE PR(SPONTANEOUS ABORTION | IN THE MITT ANALYSIS POPULATION)
###
p.sa <- seq(from = 0.08, to = 0.1, by = 0.01)

### A PLACE TO STORE THE RESULTS ###
sim.res <- matrix(NA, nrow = length(n.mitt), ncol = length(p.sa))
rownames(sim.res) <- n.mitt
colnames(sim.res) <- paste0(p.sa * 100, "%")

##################
### SIMULATION ###
##################

pb <- txtProgressBar(min = 1, max = length(n.mitt), style = 3)

for(a in 1:length(n.mitt)){

  setTxtProgressBar(pb, value = a)

  for(b in 1:length(p.sa)){
```

```
    sim.sara <- rbinom(n = n.sim, size = n.mitt[a], prob = p.sa[b])

    sara.res <- unlist(lapply(X = sim.sara, FUN = function(x, n = n.mitt[a]){

      ifelse(binom.test(x = x, n = n, p = 0.15, alternative = c("two.sided"), conf.level =
0.95)$conf.int[2] < 0.15, 1, 0)

    }))

    sim.res[a, b] <- mean(sara.res) * 100

  }

}

########################
### PLOT THE RESULTS ###
########################

### MOLD THE RESULTS FOR PLOTTING ###
sim.res.long <- data.frame(N = as.numeric(rownames(sim.res)), SA8PCT = sim.res[, 1], SA9PCT =
sim.res[, 2], SA10PCT = sim.res[, 3]) %>%
  gather(key = "SA", value = "POWER", 2:4)

p <- ggplot(sim.res.long, aes(x = N, y = POWER, group = SA)) +
  geom_hline(yintercept = 80, linetype = "dashed", color = "grey", size = 2) +
  geom_line(aes(color = SA), size = 1.5) +
  scale_x_continuous(name = "Sample Size (in MITT Analysis Population)", breaks = seq(from =
100, to = 400, by = 20)) +
  scale_y_continuous(name = "Power", limits = c(0, 100)) +
  theme(axis.text.x = element_text(angle = 45, hjust = 1)) +
  scale_color_discrete(name = "Spontaneous\nAbortion\nRate",
                       breaks = c("SA8PCT", "SA9PCT", "SA10PCT"),
                       labels = c("8%", "9%", "10%"))

######################
### TABULAR OUTPUT ###
######################

### FIND WHICH RESULTS ARE ABOVE 80% POWER ###
sim.res.80 <- sim.res >= 80

### FIND THE INDICES ###
sim.res.ind <- apply(X = sim.res.80, MARGIN = 2, FUN = function(x){
```

```
  TEMP <- length(x)
  if(any(x)){

    TEMP <- min(which(x))

  }
  TEMP

})

### REPORT THE POWER FOR THESE INDICES
sim.table <- sim.res[sim.res.ind, ]
```

Hierarchical Modeling Details

Define n_1 as the number of subjects in the current trial and Y_{1i} as the indicator of spontaneous abortion for the i^{th} subject in the current trial where $Y_1 \sim Bin(n_1, \pi_1)$. Let π_1 be the true rate of spontaneous abortions in the current trial.

The previous trial (Study DR-PGN-302) reported a spontaneous rate of abortion of 55/549. This prior information about abortion rate is incorporated into the modeling framework through a hierarchical model. Dynamic borrowing between this trial's results and the current trial's data allows borrowing to occur to the extent indicated by these two data sources. More borrowing occurs when the two rates are similar while less borrowing occurs when they differ. This "dynamic" borrowing property is distinct from other approaches which use a fixed informative prior or apriori assume an amount of borrowing between these two data sources. Let $Y_0 \sim Bin(n_0=549, \pi_0)$ where π_0 is the true rate of spontaneous abortions from the previous trial.

We transform to the logit scale for modeling purposes. Let $\theta_1 = \log(\pi_1/(1-\pi_1))$ and $\theta_0 = \log(\pi_0/(1-\pi_0))$. The hierarchical model assumes that θ_0 and θ_1 have an across studies distribution:

$$\theta_1 , \theta_0 \sim N(\mu, \tau^2)$$

The across trial mean μ and variance τ^2 are unknown and hence have a prior distribution which is combined with the data to produce estimates of μ and τ^2:

$$\mu \sim N(-2.2, 2.25)$$

$$\tau^2 \sim IG(0.125, 0.005)$$

The mean parameter μ assumes a relatively vague prior on the original scale and centered at 10%. The variance component τ^2 controls the degree of borrowing among studies. Small values of τ^2 result in a greater degree of borrowing while large values of τ^2 correspond to less borrowing. The parameter τ^2 is estimated using the data, so the observed between studies variation is a key component of the model behavior. The prior specification on τ^2 corresponds to an inverse-gamma distribution with mean 0.2 and weight 0.25.

Operating Characteristics

The planned sample size is based only on subjects that undergo fresh embryo transfer. No further drop-outs are assumed. The analysis is evaluated across a range of true effects for the current trial's spontaneous abortion rate. For the null scenario where in truth the PVR spontaneous abortion rate is 15%, 100,000 sets of trials were simulated. For all other assumed scenarios, 5,000 sets of trials were simulated.

Overall Success

We evaluated the overall probability that the 95% credible interval is entirely below 15% for each scenario of the true PVR rate. If PVR truly maintains an abortion rate below 15%, then this represents the power for achieving a credible interval entirely below 15%. If the true rate of abortions for PVR is 15%, then obtaining a credible interval entirely below 15% is the type I error. Results are provided in the table below.

True PVR Rate	8%	9%	10%	11%	12%	13%	14%	15%
Trial Success	0.979	0.933	0.830	0.670	0.485	0.297	0.167	0.084

When in truth the PVR spontaneous abortion rate is 9%, the trial has 93.3% power of achieving a 95% credible interval entirely below 15%. Alternatively, when in truth the spontaneous abortion rate is 15%, the trial has a 8.4% rate of success.

Inference Associated with Various Observed Rates

For various observed rates of spontaneous abortions, the corresponding primary analysis based on the hierarchical model is described below. The posterior mean, 95% credible interval, effective number of borrowed subjects, and the borrowing percentage (out of the n=549 subjects from the previous trial) is provided. The effective number of borrowed subjects calculation $[E(\pi_1)*(1-E(\pi_1))/Var(\pi_1)–1–240]$ is somewhat approximate as it is based on the binomial likelihood. Results are provided in the below table.

Observed Data	Estimated Rate (%) (95% CI)	Effective Number of Borrowed Subjects	Borrowing Percentage
19/240 (7.92%)	8.6% (5.7, 11.7)	103	18.9%
24/240 (10.00%)	10.0% (7.2, 13.3)	130	23.7%
36/240 (15.00%)	13.8% (10.1, 18.5)	9	1.7%

Borrowing based on the hierarchical modeling is dynamic, with higher borrowing achieved when the current trial's results are similar to the previous data and minimal borrowing when the current trial's results are at 15%. This is evidenced by both the decreasing number of borrowed subjects and the increasing width of the credible intervals. Also, based on 240 subjects being included in the analysis, the maximal number of observed responses which maintains a 95% credible interval entirely below 15% is 28.