Informed Consent Form – E4 FREEDOM

For Parents or Guardians and Adult Participants

Study Title:	A Multicenter, Open-label, Single-Arm Study to Evaluate the Contraceptive Efficacy and Safety of a Combined Oral Contraceptive Containing 15 mg Estetrol and 3 mg Drospirenone
Study #:	MIT-Es0001-C302
Sponsor:	Estetra SPRL
Study Doctor:	Michael L. Twede MD
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1.0 General Information

You are being invited to participate in a research study. It is up to you to decide if you wish to participate. Before you decide whether or not to take part in this study, we would like to explain why the research is being done and what it would involve for you. Your study doctor (who may also be your regular doctor) or member of the study staff will go through this Consent Form with you and answer any questions you might have. Ask the study doctor or member of the study staff if there is anything you do not understand. Talk to others about the study if you wish. Once you understand the study, and if you agree to take part, you will be asked to sign the Consent Form. You will be given a copy to keep. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

It is important you tell the study doctor everything regarding your health history, otherwise you may harm yourself by participating in this study.

This study is being organized and paid for by a pharmaceutical company, Estetra SPRL (the Sponsor). The Sponsor is paying the study doctor to carry out this study.

When reading this form, please note that the words “you” and “your” refer to the person in the study rather than to a parent/guardian who might sign this form on behalf of the person in the study.

2.0 Purpose of Study

The purpose of this research study is to measure how well and safe the study drug composed of 15mg Estetrol (E4) and 3mg Drospirenone (DRSP) is in preventing pregnancy. The study product is a new investigational drug. Investigational means the drug is still being tested in research studies and has not been approved for sale in the United States by the U.S. Food and

Drug Administration (FDA). It is planned that this study drug will be used as a Combined Oral Contraceptive.

A Combined Oral Contraceptive drug (commonly known as the contraceptive pill or "the pill") is based on two hormones:

- An estrogen, which contributes to contraceptive activity and causes menstrual cycles to occur regularly and predictably. Periods also tend to be lighter and shorter.
- A progestin, which prevents egg releasing from ovaries (ovulation).

The study drug is a contraceptive pill composed of a combination of Estetrol and Drospirenone:

- Estetrol, the estrogen, is a natural, sex hormone produced by the human fetus during the pregnancy. The Estetrol used in the study drug is a synthetic form and is an estrogen never used before in any Contraceptive Drug (not previously approved by the FDA).
- Drospirenone, the progestin which is widely used in marketed contraceptive pills: is associated with no water retention, no weight increase, sometimes weight loss, no blood pressure increase and fewer Pre-Menstrual symptoms. The dose employed in this study is the dose that is used when Drospirenone is incorporated into a contraceptive pill.

The results of previous clinical studies show that this combination has no ovulation, and bleeding only during the wanted period. The side effects that appeared during these clinical studies were the same as those observed during the administration of the other estrogens used in current practice.

Approximately 2000 subjects in the USA and Canada will participate in this research study.

Population Pharmacokinetic (PK) Study - Only a selection of the sites will participate in the Population PK Substudy.

In a subset of approximately 500 subjects, a substudy looking at the quantity of the study drug components E4 and DRSP in your blood will be performed. If you agree to participate in this substudy, you will be asked to confirm your willingness to participate in the signature section of this consent form. You are free to decide if you want to participate in this substudy independently of your participation in the main study, and to withdraw from the substudy at any time, without giving a reason. This would not affect the standard of care you receive or your participation in the main study.

3.0 Study Visits and Procedures

Your participation in this study will last thirteen 28-day cycles (approximately 12 months) and will include 1 Screening Visit (Visit 1 - to confirm you can participate in the study), 1 Enrollment Visit (Visit 2), 4 Dosing Visits (Visits 3 to 6) and 1 Exit Visit (Visit 7). In total you are expected to have 7 Visits over one year and 2 follow up phone calls.

At any time during the study, an Unscheduled Visit would be required if you suspect you are pregnant based on a positive urine pregnancy test performed at home, or if the study doctor judges it is necessary to examine you for a potential significant adverse event. Additional assessments can be performed at the Study Doctor's discretion.

This is an open-label and single-arm study. This means that you and your study doctor will know which study drug you will be administered and that the study drug is the same for all subjects participating in this study.

In addition to taking study drug, you will be requested to complete a diary, every day, to record the pill intake and also to record the bleeding/spotting events (if those happen), the urine pregnancy test results (when applicable), occurrence of sexual intercourse during the cycle, and use of any back-up contraceptive method (such as condom). Your diary will be reviewed with your study doctor at each visit.

You will be given blister packs which each containing 28 pills: 24 pink pills (active substance - Estetrol 15mg / Drospirenone 3mg) and 4 white placebo pills (inactive substance). The study drug must be taken at approximately the same time of the day across the dosing period. This regimen will allow you to avoid inadvertently missing intake of pills during the dosing period.

3.1 Procedures

This clinical study requires 7 visits to the study clinic over a period of 13 cycles of 28-days (i.e. 12 months). Study Visits will be conducted as indicated below:

- **Visit #1:** Screening visit (eligibility check),
- **Visit #2:** Enrollment visit within 30 days from previous visit,
- **Visit #3:** between day 1 and 14 of your cycle 2,
- **Visit #4:** between day 1 and 14 of your cycle 4,
- **Visit #5:** between day 1 and 14 of your cycle 7,
- **Visit #6:** between day 1 and 14 of your cycle 10,
- **Visit #7:** between day 16 and 23 of your cycle 14, or earlier if your participation is terminated in advance.
- At any time during the study, an **Unscheduled Visit** could occur. An Unscheduled Visit would be required if you suspect you are pregnant based on a positive urine pregnancy test performed at home, or if the study doctor judges it is necessary to examine you for a potential significant adverse event. Additional assessments can be performed at the Study Doctor's discretion.

During the visits, the Study Doctor or Study Staff will complete the following tests and procedures:

- Signature of **informed consent form** document (Visit #1) to confirm your willingness to participate to this clinical research;
- Review of your **eligibility** (Visit #1 and #2) – Your Study Doctor will check the eligibility criteria of the protocol to decide whether your participation is possible or not;
- Collection of your **demographic data** such as your age and ethnic origin (Visit #1);
- Review of your **medical and surgical history** (Visit #1) – Your Study Doctor will discuss with you your current health status, will check if you have any cardiovascular risk factor(s) and if you had any surgical procedure(s) in the past. It is important that you answer all of these screening questions truthfully and completely;

- Review of your **gynecological history** (Visit #1) – Your Study Doctor will review with you some information related to any pain during menstruation, menstrual cycle length (if this is the first time you are taking a contraceptive drug), previous contraceptive methods used and any history of pregnancy including if any during hormonal contraceptive use;
- Review of any previous and **current medications** you are (or have been) taking (all Visits);
- **Physical examination** (Visits #1 and #7) – Your Study Doctor or Study Staff will examine your body as a whole. No rectal examination will be performed;
- **Weight** measurement (Visits #1, #4, #5 and #7) and **Height** measurement (Visit #1);
- **Gynecological examination** (Visits #1 and #7) – This examination will be performed by your Study Doctor twice during the study and includes your breast to be examined by palpation (this is touching and feeling your breasts);
- **Cervical cytology** (Visit #1) – This test will be performed on all women older than 20 years only if you did not have it in the past 18 months or the result of your last test is unavailable. A small number of cells from your cervix will be removed using a tiny brush; this test is also called Pap test. These cells will be examined under microscope in the laboratory. If the results of your test at Screening visit (Visit #1) show an abnormality, you cannot be enrolled in this study;
- **Chlamydia/gonorrhea testing** (Visit #1 and at Visits #2, #3, #4, #5, and #6 if you report a change in sexual partner between two visits): During gynecological examination a vaginal swab will be obtained to look for bacteria called Chlamydia and Gonococcus. A vaginal swab test involves taking a sample of vaginal secretions with a device that looks like a cotton bud. The secretions are then placed in a special container and sent to the microbiology laboratory for further analysis.
    - The study doctor or study staff will tell you if the test results are positive.
    - Please note that if you are the parent or guardian of a child in this study, the study doctor and study staff may or may not tell you the results of this testing, depending on state law.
    - If required by state law, the study doctor or study staff may report a positive test result to the local health department.
    - The results of these tests must be negative in order for you to be in the study.

  If your result is positive, you will be treated prior to enrollment into the study and during the study if needed. Your Study Doctor will choose the appropriate treatment, which will be paid for through your healthcare provider.
- **Serum pregnancy test:** (Visits #1 and #7) - Approximately 1 teaspoon (5 ml) of your blood will be taken. To be eligible to take part in this study, the pregnancy test must be negative.
    - The study doctor or study staff will tell you if the pregnancy test results are positive.
    - Please note that if you are the parent or guardian of a child in this study, the study doctor and study staff may or may not tell you the results of your daughter's pregnancy testing, depending on state law.
- **Enrollment confirmation** (Visit #2) - Your Study Doctor will confirm your eligibility after review of your medical history and the laboratory results;
- Receive **home urine pregnancy test kits** (Visit #2) – You will be asked to perform a urine pregnancy test, in the morning prior to the first pink tablet intake to ensure you are

not pregnant before you start taking the study drug. You will have to record the result in your diary. If your test is negative, it means you are not pregnant and you can start the study drug. If your test is positive you should not take any study drug and immediately contact your study doctor, who will invite you for an unscheduled visit to confirm your pregnancy by performing a blood pregnancy test to confirm the pregnancy and if applicable, an Ultrasound to confirm the date of conception. You will also receive additional pregnancy tests in the case you suspect you may be pregnant during the study. If the test is positive, you should stop taking the study drug and contact the study staff immediately;

- **Blood samplings** (Visits #1, #5 and #7) - You will have approximately 2.5 teaspoons (12 ml) of your blood collected 3 times during the conduct of the study; to assess the safety parameters. You should not have eaten (fast) for 8 hours (no food or beverages except water) before each blood collection. You can and should drink pure water as usually. The reason for fasting prior to a blood test is so that food and beverages do not influence your test ratings. No fasting is required until after you have signed the consent form. It is possible that you will need to return to the study center to complete visit 1. Altogether approximately 7.5 teaspoons (36 ml) of blood may be drawn during the study;
- **Vital signs** (Visits #1, #2, #3, #4, #5, #6 and #7) – Your blood pressure and your heart rate will be measured while you are sitting for at least 5 minutes;
- Receipt of your **study drug** (Visits #2, #4, #5 and #6) – You will receive 3 or 4 blisters, that is, doses for 3 or 4 cycles. You will take the first pill of this study drug after Visit #2 following specific instructions which will be provided to you by your Study Doctor or Study Staff. You will need to take 1 pill each day, approximately at same time of the day. At Visit #2, you will receive a spare blister (so in total 5 blisters at this visit) in case you encounter any issues. Seven days after you have started taking the study drug, your Study Doctor or Study Staff will phone you to help you in the Diary completion (see below). You will receive instructions how to use it and what to do in case you miss any pills. Additionally, you will be instructed to come back with all your study drugs (used or not including spare) at the next visit;
- **Receive your Diary**. (Visit #2) - You will be given a Diary with instructions on how and when to complete it. You will be explained how to complete it and instructed to always bring it with you at each visit;
- **Collect your study drug** (Visits #3, #4, #5, #6 and #7) - Your Study Doctor and Study Staff will verify if you have taken the pills according to the instructions;
- **Collect and review of completed pages of your Diary** (Visits #3, #4, #5, #6 and #7) – the study staff will take the completed pages of the Diary and will review them with you;
- Receive your **quality of life questionnaire and menstrual distress questionnaire** (Visits #2 and #6) – you will receive instructions on how to complete the documents. These questionnaires will allow the Sponsor to assess your well-being and symptoms you may have before and during your menstruation;
- **Collect and review of quality of life questionnaire and menstrual distress questionnaire** (Visits #3 and #7) – the site staff will collect the completed questionnaires and will review them with you;
- **Contraceptive counseling** (Visits #6 and follow-up call) - You will discuss with the Study Doctor the contraception method you could use when the study is finished. You

will also be called by phone when you are supposed to start your next contraceptive method.
- Review of any **adverse events** and **modifications of your well-being** if noticed since the last visit (all Visits);
- **Follow-up call** (Visit #6) – Your Study Doctor or Study Staff will phone you on the day (+/- 1 day) you are expected to start your next contraceptive method to ensure you have started it;
- **End of study form** (Visit #7) - This form will be completed by your Study Doctor or Study staff to close of your study participation.

In case you wish to become pregnant, please discuss with the study staff. You will stop the study drug and be discontinued from the study. However, your Study Doctor or Study Staff will call you every 6 to 8 weeks and for a maximum of one year until your menses have returned and until you are pregnant or if you started another contraceptive method.

PK Substudy

Additional blood samples will be collected to see how much study drug is in your blood. This is called pharmacokinetics (PK).

- **Blood samplings** (Visits #3, #4 between Days 10 and 14 of cycles 2 and 4) - Each visit will last a minimum of two hours; a first blood sample will be collected shortly upon your arrival and another one two hours later. You will have approximately 1.8 teaspoons (9 ml) of your blood collected 2 times during each visit to assess the quantity of the study drug components in your blood (PK). Altogether, in addition to the blood collected for safety parameters, approximately 7.5 teaspoons (36 ml) of blood may be drawn during the study for the PK assessments.
- **Study drug intake on site** (Visits #3, #4 between Days 10 and 14 of cycle 2 and 4) – depending on the time you usually take your study drug and the time you have your appointment for each visit, you may be asked by the Study Staff to take your Study Drug after the first blood sampling. You will receive clear instructions from the Study Staff at the time of the visit scheduling. You will be asked to record in your Diary for these cycles, the time you have taken the last Study Drug before the visit.

4.0 Subject Responsibilities

If you decide to participate in this study, there are certain responsibilities that you have before, during, and after the study period. Some are listed below, but there could be others that the study doctor will discuss with you:

- At the beginning of the study, you should tell the Study Doctor all the information you know about your health and all medications (prescription or non-prescription) that you are currently taking. If you do not tell the Study Doctor everything you know, you may put your health at risk.

- You should not start taking any prescription or non-prescription medications without the agreement of the Study Doctor. There are some medications you will be asked not to take at all during the study, and others that you cannot take at certain times during the study. The Study Doctor will explain this to you in more detail.
- You must take the study drug as instructed and return all of used and unused study drug and/or study materials (for example, questionnaires, diary's pages).
- You must follow all instructions given to you while you are participating in this study. If you do not follow the instructions, you may be removed from the study. If you are unsure about what you are supposed to do, ask the Study Doctor.
- You must report all side effects and medical problems to the study staff.
- You must complete the diary on a daily basis.
- Any use of contraceptive methods other than study drug during the period of the study must be recorded in the diary.
- During the study at two different times (beginning and end of the study), you must complete two questionnaires (quality of life questionnaire and menstrual distress questionnaire).
- If you decide to withdraw from participating, you must inform the study doctor or staff. You will be required to complete an early termination visit. If you fail to return for a scheduled visit, your Study Doctor or the Study Staff will contact you twice by phone to confirm the reason for not returning and if no response, your Study Doctor will send you a letter by registered mail. Withdrawal of the study will not have a negative influence on your relationship with your Study Doctor and on your future medical care and treatment.

5.0 Potential Benefits

The information that is obtained during this study may be useful scientifically and thus be helpful to others requiring the same contraceptive method.

You may or you may not benefit from participating in this study. If you agree to participate in this study you will take study drug that contains a synthetic form of a natural estrogen named Estetrol. Previous studies have demonstrated that the use of combination of Estetrol and Drospirenone has a good contraceptive efficacy; your menstrual cycles may occur regularly and predictably, periods have also tended to be lighter and shorter. The study drug was also well tolerated.

6.0 Potential Risks and/or Discomforts

Please keep in mind that even when taking the modern contraceptive pills there is a small risk of getting pregnant.

The following side effects were observed following the oral intake of this study drug (Estetrol 15mg / Drospirenone 3mg). Therefore, by participating to this study you may have some of these side effects.

Common side effects (observed in less than 10% of women):

- Vulvovaginal dryness, discharge and infection;

- Decreased libido (sex drive) or loss of libido;
- Irritability, mood swings;
- Migraine, headache;
- Abdominal distension, upper abdominal pain, nausea, vomiting;
- Painful or excessive menstruation;
- Breast swelling, tenderness, or pain;
- Acne;
- Night sweats.

You might have side effects or discomfort, which are not listed above. Ask the study doctor if you have questions about the signs or symptoms of any side effects that you read about in this consent form. Some side effects may not be known yet. Tell you Study Doctor or Study Staff right away if you experience any such effects or discomfort. Please tell them if you have any other problems with your health or the way you feel during the study, whether or not you think these problems are related to the study drug.

For your information, other side effects were reported by women using a marketed contraceptive pill containing Drospirenone as progestin such as Yaz® (20 µg Ethinylestradiol / 3 mg Drospirenone):

Common side effects (observed in more than one woman in **100** but in less than one woman in **10**)	Uncommon side effects (observed in more than one woman in **1000** but in less than one woman in **100**)	Rare side effects (observed in more than one woman in **10,000** but in less than one woman in **1000**)
• emotional lability (irritability) • headache • nausea • breast pain • excessive or absence of menstruation	• depression, nervousness, somnolence (drowsiness) • asthenia (weakening) • dizziness • paresthesia (sensation of tingling) • migraine • varicose vein • hypertension, • abdominal pain, vomiting, indigestion, flatulence, gastritis, diarrhea • acne, pruritus, rash • back pain, pain in extremity, muscle cramps • vaginal infection, vaginitis, genital discharge, vaginal dryness • pelvic pain • breast enlargement, fibrocystic breast	• anemia, low blood level of platelets • allergic reaction • endocrine disorder, increased appetite or loss of appetite • high blood level of potassium, low blood level of sodium • absence of orgasm, • insomnia, vertigo, tremor, • malaise • conjunctivitis, dry eye, eye disorder, • tachycardia (abnormal rapid heart rate), • phlebitis (vein inflammation), vascular disorder, nose bleed, syncope, venous thromboembolism (blood clot), arterial thromboembolism, • abdomen enlarged, gastrointestinal disorder, or fullness

	• menstrual disorder including: uterine/vaginal bleeding (bleeding irregularities), excessive or light menses, painful menstruation • hot flushes • suspicious Pap smear • libido decreased • sweating increased • edema (swelling) • weight increased	• hiatus hernia • constipation • oral infection, dry mouth • biliary pain, cholecystitis (gall bladder inflammation) • skin disorders such as chloasma, eczema, alopecia, dermatitis acneiform, dry skin, erythema nodosum, hypertrichosis, skin striae, contact dermatitis, photosensitive dermatitis, skin nodule • painful sexual intercourse, vulvovaginitis, bleeding after sexual intercourse, withdrawal bleeding • breast cyst, hyperplasia (increased cell production), or neoplasm • cervical polyp, endometrial atrophy, ovarian cyst, uterine enlargement • weight decrease

If I stop the dose of my regular medications, what are the risks?

If you stop the dose of your regular medications to be in the study, your health might get worse. Please tell the study doctor or study staff right away if you have any problems when you stop or change your regular medications.

Other medications, supplements, or vaccines taken together with this study drug may increase the chance of unwanted effects. The risk will depend on how much of each medication you take every day, and on how long you take the medications and study drug together. It is very important that you tell the study doctor about any medications, supplements, or vaccines before you take them during the study. If your Study Doctor instructs you to take these medicines together with the study drug on a regular basis, follow his or her directions carefully.

Other Risks Related to Study Procedures:

Blood Draw

Several blood samples will be collected during this study. A needle is inserted into a vein in the arm and a small blood sample is withdrawn. Although one blood draw is usually sufficient, a second one may be necessary if the first is not successful. Collecting blood samples may cause fainting, dizziness, and some light pain and/or bruising at the site on your arm where the blood was taken. In very rare occasions, infection may occur. The laboratory blood tests will require approximately 7.5 teaspoons (36 ml) of your blood to be drawn.

PK Substudy

In addition to the blood collected for safety parameters, approximately 7.5 teaspoons (36 ml) of blood may be drawn during the study for the PK assessments.

Gynecological examination, Chlamydia, Gonorrhea and Cytological tests

You will be examined by a gynecologist and during this examination a vaginal secretion will be obtained to look for the presence of some bacteria (called Chlamydia and Gonococcus). Usually the gynecological examination and vaginal secretion sampling don't cause any pain but some women experience discomfort during the examination and procedure. Most people who have chlamydia or Gonococcus have no symptoms, but if not treated, the infections can cause serious complications.

During this gynecological examination a cervical cancer screening test, which is also called a Pap test, may be performed if you are older than 20 years and if you did not have any in the past 18 months. A small number of cells are removed from your cervix using a tiny brush. These cells are then examined under microscope in a laboratory for any type of abnormalities. While the procedure typically does not cause complications, it is possible to have temporary pelvic discomfort, pressure or slight pain while your study doctor removes cervical cells, and discomfort or bleeding after the test. Vaginal bleeding is typically mild and stops within a day.

The study drug does not provide protection against sexually transmitted infections including HIV, Hepatitis B, herpes simplex or syphilis infections.

Sensitivities

You cannot participate in the study if you are allergic or sensitive to estrogen and progestin products, including natural supplements with progestin-like or estrogenic action, for example phytoestrogens. Since there are several components in the study drug, please discuss with the Study Doctor any allergy or sensitivity you have, for example lactose.

Questionnaires and Diaries

Filling out the questionnaires and diaries, and answering the study doctor or study staff's questions could lead you to feel uncomfortable or upset. Please tell the study doctor or study staff if you feel uncomfortable or upset while filling out a questionnaire or diary, or answering questions. You have the right to refuse to answer any questions.

There is a risk of loss of confidentiality of your information. You will read more about the protection of your information later in this form. Please ask the study doctor or study staff if you would like to know more about how your information will be protected while you are in this study.

7.0 Cautions and Warnings

Serious allergic reactions, that can be life threatening, may occur when taking any medication including the study drug. If you have a very bad allergic reaction, you could die. Some things that happen during an allergic reaction that could be a sign or symptom of a life-threatening allergic reaction (anaphylaxis) are:

- a rash
- a fast pulse
- sweating
- a feeling of dread
- swelling around the eyes and mouth
- swelling of the throat
- wheezing
- having a hard time breathing
- a sudden drop in blood pressure (making you feel dizzy or lightheaded)
- inability to breathe without assistance

You should get medical help and contact the study doctor or study staff if you have any of these or any other side effects during the study.

All study drug must be taken only by the study participant.

The study drug is not in a package that is resistant to opening by children. Keep all medications out of reach of children.

8.0 Pregnancy/Birth Control

As with all contraceptive pills, there is a risk of getting pregnant. However, if pills are taken according to the instructions given, the risk of getting pregnant is small.

Estetrol is a natural human hormone, produced by the fetal liver during pregnancy only. However the risk of taking a combination of a synthetic form of Estetrol and Drospirenone by pregnant women and its influence on a fetus is unknown so far. Some drugs cause premature (early) birth or birth defects.

For this reason, it is essential that you follow instructions from your study doctor and take study drugs carefully to avoid becoming pregnant. At present, there is not enough available data to guarantee that this study drug does not involve any risks for a baby while breast-feeding.

You must perform a urine pregnancy test before receiving the first dose of the study drug. You must also perform a urinary pregnancy test if you think you may be pregnant. If the result of this test is positive, you must contact the study doctor immediately. Your study doctor will invite you for an unscheduled visit to confirm your pregnancy by performing a blood pregnancy test and an ultrasound, if applicable, to confirm the date of conception. Your study doctor will follow-up on the progress of your pregnancy until the baby is born.

If you suspect that you have become pregnant while participating in the study and if your urine pregnancy test is positive, you must notify your study doctor immediately and you will be invited to visit your study doctor as soon as possible. Following confirmation of the pregnancy you will

have to withdraw from participation in this study and the study staff will discuss your options with you:

- Should you choose to continue with the pregnancy, the study staff and sponsor need to collect some safety information about your pregnancy and your baby;
- Should you want not to continue with the pregnancy, appropriate options should be discussed with the Study Doctor. In case you don't want to continue with the pregnancy, the sponsor needs to collect some information related to the abortion.

COULD I HAVE ANY OTHER PROBLEMS WITH MY HEALTH IF I AM IN THIS STUDY?

It is possible that you could have problems and side effects of Estetrol 15mg / Drospirenone 3mg that nobody knows about yet.

Ask the study doctor if you have questions about the signs or symptoms of any side effects that you read about in this consent form.

9.0 Will I Receive Any New Information During the Study?

If the study doctor or study staff learns any new information that might change your mind about continuing in the study, the study doctor or study staff will tell you about it.

10.0 Reimbursement/Cost for Participation

You/your child will get a total of up to $525 if you finish the whole study. If you/your child does not finish the whole study, you/your child will get $75 for each study visit you/your child finish. If applicable you will get $75 for any unscheduled study visits you finish. The study doctor or study staff can tell you more about when you/your child will get paid.

The study is being sponsored by Estetra SPRL (the Sponsor). The Sponsor will be responsible for the cost of the study drug and all of the examinations and assessments that are part of the study.

The study drug will be given to you free of charge, and you will not have to pay for any clinic visits or for any tests required by the study. Should you discontinue the study early, or if you are discontinued early by your Study Doctor or the Sponsor, you will be compensated only for the number of completed visits.

Any health expenses not related to the study will not be covered by the Sponsor. **Before you agree to be in this study, you should contact your health-care payer/insurer to see if your plan will cover the costs required as part of your participation.** For example, if you test positive for Chlamydia/gonorrhea and require treatment in order to participate in the study, the cost of this treatment is not paid for by the Sponsor. You can ask the study doctor or study staff to find out more about costs.

11.0 Alternatives

If you do not wish to participate in this study, you will continue to be treated by your regular doctor and your care will not be affected in any way. Your regular doctor may continue with your current treatment regimen or modify it. Before you decide to participate in the study, you should know that other contraceptive methods are available on the market: combined oral contraceptives, hormonal vaginal ring, transdermal patch, injectable hormonal methods, dermally implantable hormonal method and other methods like progestin-only pills, intrauterine device or intrauterine system, condoms, etc. There are benefits and risks associated with these contraceptive methods that should be discussed with your study doctor. In addition, you may discuss your options with your regular health care provider.

12.0 Biological samples

All samples (urine, blood, swab) will be collected by the study staff. These samples will be processed in a secure laboratory.

Samples are only identified by the study and your code numbers. Your samples will not be labeled with your name or other directly identifying information. The list that matches the code with your name and information will be stored separately from your samples.

Any left-over samples (serum or plasma obtained from blood) obtained during the study belonging to you may be stored until the product is on the market. These samples may be used by the Sponsor or by other companies belonging to the Sponsor for future research on the study product E4/DRSP. No characterization of human genetic material will be undertaken.

You have the right to oppose the use of your blood samples for future research. You will state whether or not you want your blood samples used for future research on the signature page of this form. Such opposition will not affect your participation in this (or future) study(ies). However, if you had agreed to future use of your blood samples, but later changed your mind, you must ask for the samples to be destroyed before your participation in the study ends.

You will not be entitled to any right of ownership in any inventions or profits that might arise from any use of these samples.

13.0 Confidentiality and Processing of Participant's Personal Information

This section explains who will use and share your health information if you agree to be in this study. You must authorize this use and sharing of your information by signing this form or you cannot be in the study. You can still be in the main part of the study even if you do not authorize the use and sharing of your information for the optional part(s) of the study.

The study doctor and study staff will collect, use, and share health information about you, including any information needed to do the study and other identifying information about you, such as your name, address, phone number, or social security number. The information used and shared will include:

- information from your medical records
- information collected about you during the research

All reasonable measures to protect the confidentiality of your study records and your identity will be taken to the extent permitted by the applicable laws and/or regulations, and will not be made publicly available. HIPAA Regulations or applicable state law requires that you authorize the release of any health information that may reveal your identity.

The persons and entities that you are authorizing to use or disclose your individually identifiable health information may include:

- the study doctor, the study staff, and the study center.
- Estetra SPRL and all applicable parties who work with the sponsor.

In order to analyze the data collected during this research study, all of the health information generated or collected about you during the study may be inspected by the study Sponsor or the authorized agents of the Sponsor, the FDA, the Department of Health and Human Services (DHHS) other government regulatory agencies from other countries, and Quorum Review as well by representatives of Estetra SPRL or their designee (PRA Health Sciences).

Regulatory agencies are required by law to review the quality and safety of research.

Your information may also be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability, and conducting public health surveillance, investigations, or interventions.

After your information is shared with the people and companies listed above, the law may not require them to protect the privacy of your information. To maintain the integrity of this research, you might not have access to any health information developed as part of this study until it is completed. At that point, you generally would have access to your health information.

The results of this study may be presented at meetings or in publications; however, your identity will not be disclosed in these presentations. By signing this informed consent form, you are authorizing such access to your medical records.

This authorization will expire in 50 years.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

You may also revoke the authorization to use or disclose personal information about your health. If you choose to withdraw your authorization, you must notify the study doctor in writing.

If you cancel your authorization, you will not be able to continue in the study. You can cancel your authorization for the optional part(s) of the study and remain in the main study.

If you cancel your authorization, the study doctor and study staff will still be able to use and share your information that they have already collected.

14.0 Voluntary Participation and Termination of Participation

Your participation in this research study is voluntary. You can choose not to participate in this study either at the beginning or at any time during the study. Your choice will not have an

adverse impact on your present or future health care. There will be no penalty or loss of benefits to which you are otherwise entitled. To ensure your safety, you will be asked to undergo a final evaluation visit. If you wish to withdraw from the study, you should contact the study doctor or study personnel at the phone number listed on page 1 of this form.

The study doctor will still be able to use the information collected about you prior to your withdrawal from the study. Information that has already been sent to the study Sponsor cannot be withdrawn.

Your participation in this study may be discontinued without your consent by the study doctor or the Sponsor if you fail to follow the study doctor's instructions. You may also be withdrawn from the study if, in the study doctor's opinion, the study drug is ineffective, harmful, or has medically unacceptable side effects, or for other reasons at the discretion of the Estetra SPRL or the study doctor. If you are withdrawn from the study, you will be asked to have the appropriate medical tests and follow-up to evaluate your health and safety.

15.0 Injury Compensation

Before participating you should consider if this will affect any insurance you have and seek advice if necessary.

In the event of an illness or injury that is determined to be directly related to the administration of study drug or the properly-performed study procedures, the Sponsor, Estetra SPRL, agrees to pay all reasonable and necessary medical expenses to treat such illness or injury provided that you have followed the directions of the study doctor, and that you have not otherwise been reimbursed by your personal insurance, a government program, or other third party coverage for such medical expenses. No other compensation will be offered by the Sponsor or the Institution. Financial compensation for such things as lost wages, disability, or discomfort due to any research-related injury has not been made available. By signing this form, you are not waiving any legal right to seek additional compensation through the courts.

Be aware that your health care payer/insurer might not cover the costs of study-related injuries or illnesses.

16.0 Who to Contact to Ask Questions or Report a Possible Research Related Injury or Reaction

If you have any questions concerning your participation in this study, or if you feel you have experienced a research-related injury or a reaction to the study drug, you should contact the study doctor or study staff at the phone number listed on page 1 of this form.

17.0 Who to Contact To Report a Breach of Confidential Information

If you feel that there has been a breach of your confidential information, you should contact the study doctor or study staff at the phone number listed on page 1 of this form.

18.0 Who to Contact to Ask Questions About Your Rights as a Research Subject

In the event of an emergency, dial 911 immediately.

If you require emergency care, be sure to tell the emergency care provider about your participation in this study. Contact the study doctor or study staff as soon as possible.

You can ask questions about the study at any time. You can call the study doctor or study staff at any time if you have any concerns or complaints. You should call the study doctor or study staff at the phone number listed on page 1 of this form if you have questions about the study procedures, study costs (if any), study payment (if any), or if you get hurt or sick during the study.

Quorum Review reviewed this study. Quorum Review is a group of people who review research studies to protect the rights and welfare of research participants. Review by Quorum Review does not mean that the study is without risks. If you have questions about your rights as a research participant, if you are not able to resolve your concerns with the study doctor or study staff, if you have a complaint, or if you have general questions about what it means to be in a research study, you can call Quorum Review or visit the Quorum Review website at www.quorumreview.com.

> Quorum Review is located in Seattle, Washington.
> Office hours are 8:00 AM to 5:00 PM Pacific Time, Monday through Friday.
> Ask to speak with a Research Participant Liaison at 888-776-9115 (toll free).

19.0 Consent

I have read this form, and I have been able to ask questions about this study. The study doctor or study staff has talked with me about this study. They have answered all my questions. I voluntarily agree to be in this study. I agree to allow the collection, use, and sharing of my information as described above.

By signing this form, I do not give up any of my legal rights. I will get a signed copy of this consent form.

Do you want the regular doctor to be informed about your participation?

- I accept that my general practitioner is to be informed of my participation in the study. (If you say “no,” you can still be in the study.)

  ☐ You have my permission to contact my general practitioner to let him or her know that I am participating in this study.

  ☐ You **do not** have my permission to contact my general practitioner to let him or her know that I am participating in this study.

Do you want left-over samples used for future research?

- I accept that the left-over biological samples may be used in the future for additional analysis in the context of this project: (If you say "no," you can still be in the study.)

  ☐ Yes

  ☐ No

Do you want to participate in the PK substudy?

- I (please tick appropriate box) will/will not participate in the PK Substudy. (If you say "no," you can still be in the main study.)

  ☐ Yes, I agree to have extra blood taken for the PK testing.
  ☐ No, I do not agree to have extra blood taken for the PK testing.

  ☐ The study doctor or study staff have told me my study center is not doing the PK testing.

- I have read the description of the clinical research study and have had it explained to me in words and terms that I understand. I understand that my participation is voluntary.
- The study doctor in charge of the study will inform me of any new findings developed during the course of this study, which may affect my willingness to allow my continued participation.
- I authorize the release of my study-related medical records to the Sponsor, or the authorized agent of the Sponsor, the regulatory authorities, and Quorum Review.
- By signing this form, I authorize the collection, use, transfer to other countries, storage of my personal information and medical data in databases and disclosure, as notified by this form, under a duty of confidentiality.

_____
Printed Name of Participant

_____ _____
Signature of Participant (if an Adult) Date

_____
Participant's City, State, ZIP>>

If participant does not have the legal capacity to consent to their participation:

I am the parent/guardian of the participant named above and I consent to her participation in this research study. I also authorize the collection, use and sharing of the participant's information.

_____
Printed Name of Parent/Guardian

_____ _____
Signature of Parent/Guardian Date

I attest that the individual providing consent had enough time to consider this information, had an opportunity to ask questions, and voluntarily agreed to participation in this study.

_____
Printed Name of Person Explaining Consent

_____ _____
Signature of Person Explaining Consent Date