Official Title: Elagolix for Fertility Enhancement Clinical Trial (EFFECT)
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Informed Consent

Department/Section of Obstetrics and Gynecology

ELAGOLIX FOR FERTILITY ENHANCEMENT TRIAL (EFFECT)

Informed Consent Form to Participate in Research

Bruce A. Lessey MD, PhD, Principal Investigator

SUMMARY

You are invited to participate in a research study. The purpose of this research is to study a drug called elagolix (ABT-620) for the treatment of infertility and IVF failure. You are invited to be in this study because you are a woman age 18 to 42 who may have endometriosis and infertility who is planning to transfer a normal (euploid) embryo in the future. Your participation in this research will involve 4 to 5 visits and last about 3 to 4 months.

Participation in this study will involve being randomized to receive either elagolix or a standard oral contraceptive (birth control pill) every day for 2 months. All research studies involve some risks. A risk to this study that you should be aware of is that you might experience side effects of the treatments, including headache, nausea or hot flashes. There is the possibility that you may benefit from participation in this study.

Your participation in this study is voluntary. You do not have to participate in this study if you do not want to. There may be other choices available to you. Some other choices may include under-going embryo transfer without prior treatment. You will not lose any services, benefits, or rights you would normally have if you choose not to participate.

The remainder of this form contains a more complete description of this study. Please read this description carefully. You can ask any questions if you need help deciding whether to join the study. The person in charge of this study is Bruce A Lessey MD, PhD. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study his/her contact information is: Bruce A Lessey, MD, PhD, [redacted] Ph [redacted].

If you have any questions, suggestions or concerns about your rights as a volunteer in this research, contact the Institutional Review Board at [redacted] or the Research Subject Advocate at Wake Forest at [redacted].

INTRODUCTION

You are invited to be in a research study. Research studies are designed to gain scientific knowledge that may help other people in the future. You are being asked to take part in this study because you have Infertility and tested positive for biomarkers of endometriosis and you are contemplating a future transfer of an embryo. Your participation is voluntary. Please take your time in making your decision as to whether or not you wish to participate. Ask your study doctor or the study staff to explain any words or information contained in this informed consent document that you do not understand. You may also discuss the study with your friends and family.

WHY IS THIS STUDY BEING DONE?

The purpose of this research study is to test whether a drug used to treat endometriosis associated pain can be helpful for enhancing fertility in the setting of In Vitro Fertilization and Embryo Transfer (IVF-ET). Elagolix is a drug that reduces estrogen and can improve symptoms of endometriosis. One of those symptoms is infertility and implantation failure. Elagolix has been approved by the US Food and Drug Administration (FDA) for the treatment of pain and endometriosis, but it has not been approved for use for fertility enhancement.

In this study elagolix will be compared to birth control pills (OCPs). In this study you will either receive the active study medication, elagolix or OCPs.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

100 people at 3 research sites will be needed to compete this study, including approximately 40 to 50 number people at this research site. In order to identify the necessary number of subjects needed here, we may need to screen as many as 100 subjects, since some people will not qualify to be included in the study and others may decide not to be randomized. We expect that up to 50 subjects may be non-randomized controls.

WHAT IS INVOLVED IN THE STUDY?

You are eligible for this study because you previous had an unsuccessful embryo transfer and you have tested positive for two biomarkers of endometriosis, BCL6 and SIRT1. Because you have normal (euploid) frozen embryos and are planning to undergo a frozen embryo transfer (FET) in the future, you are eligible to be part of this study.

If you agree to participate, you will be randomized into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. You will have an equal chance of being placed in either group.

The treatment study will consist of 4 phases:

1) The consent process
2) Randomization to one of two treatment groups

3) Treatment with elagolix or OCPs for 2 months
4) Frozen embryo transfer cycle

Your participation will last approximately 3 to 4 months and include 5 extra clinic visits.

If you qualify to participate in this study, you will be randomly assigned by chance (like flipping a coin) to receive the study drug, elagolix or birth control pills.

Procedures:
If you agree to be in the study, you will undergo some procedures and activities. These include performing a blood test for hCG (human menopausal gonadotropin) to rule out pregnancy and blood will be collected and stored for measurements related to inflammation (cytokines). Other products in blood (white blood cells) will be collected for measurements on micro ribonucleic acids (miRNAs), as a blood test for endometriosis. If you receive elagolix, you will be asked to take 1 pill twice a day, either 1 hour before a meal or 2 hours after a meal. If you are in the OCP group, you will be asked to take 1 pill a day 1 hour before a meal or 2 hours after a meal. The medications will be prescribed for 2 months, but you will come in after 1 month to evaluate you for any side-effects you might be experiencing. We will ask you to keep a daily diary of any side-effects you might be experiencing.

Blood drawing
You will have approximately 3 tablespoons of blood withdrawn from a vein at the beginning and end of the treatments.

Visits:

Visit 1: Screening and enrollment. Following initial screening of potential subjects with an IVF failure and available euploid embryos for transfer, patients will meet with the research nurse who will review all inclusion and exclusion criteria and obtain informed consent from eligible patients. Patients with positive BCL6 and SIRT1 on previous endometrial biopsy with failed IVF and available embryos intending FET will be consented.

Visit 2 First day of your period (menses). Patients will be instructed to call with the menses at which time an hCG measurement and a blood draw will be performed. Subjects will be prepared for their two treatment cycles. Patients will be randomized using computer generated assignments to receive 200 mg of elagolix twice daily or daily OCPs (orthocyclin).

Visit 3: All subjects will be seen at 1 month time interval and the daily diary reviewed and adverse reactions recorded. The second month of medications will be dispersed at that time.

Visit 4: After completion of 2 months of treatment with elagolix or OCPs, subjects will return for collection of blood (serum and plasma which will be collected, processed and stored at -80° C for later evaluation. Subjects will be prepared for the upcoming FET

cycle.

Visit 5: Completion of the study. Patients will return periodically for standardized treatments as part of their FET cycle for endometrial preparation, ultrasound and embryo transfer as dictated by the clinicians in the practice.

Visit 6: Subjects will return 8 to 9 days after embryo transfer for a pregnancy test. hCG levels and progesterone levels will be recorded. Follow-up ultrasounds performed for pregnancy monitoring will be examines and pregnancy outcomes will be recorded and/or extracted from their SART database for pregnancy included extended follow-up for live birth rate, obtained from SART database.

If you choose to be in the control group, you will have the standard embryo transfer protocol.

We can send copies of your test results to your personal physician. Even if you do not wish to have any of your medical information sent to your physician, you can still participate in this research study.

Do you request that we send important medical findings from your study tests/exams to your personal physician?

[ ] Yes [ ] No _____ Initials

STORAGE of Biological Specimens ***(insert the following section if you will STORE biological samples for use in future research)***

If you agree to participate in this study, we will (draw 3 tablespoons of the blood) to use for future research. This sample will be kept and may be used in future research to learn more about other diseases. Your sample will be obtained (at the CFEM clinic) at Wake Forest University Baptist Medical Center. The sample will be stored in the Research Laboratory at Watlington Hall and will be given only to researchers approved by (PI of study). An Institutional Review Board (IRB) must also approve any future research study using your tissue sample. In order to participate in this study, you must be willing to provide this sample for future research.

The research that may be performed with your blood/tissue sample is not designed to help you specifically. There is no personal benefit to you from taking part in this aspect of the research study. It might help people who have diseases at some point in the future, but it is not known if this will happen. The results of the research performed with your blood /tissue will not be given to you or your doctor. The results will not be put in your medical record. The research using your blood/tissue sample will not affect your care.

Your blood/tissue sample will be used only for research and will not be sold. The findings from

this research may result in the future development of products that are of commercial value. There are no plans to share any of the profits with you which may occur as a result of the research.

Your *blood/tissue* sample will be stored with a unique identifier and will not include any identifiable information about you such as your name, address, telephone number, social security number, medical record number or any of the identifiers outlined in the HIPAA Privacy Rule. The unique identifier will be a randomly assigned number and only the principal investigator will have access to the code that links the unique identifier to you. Your name, address, social security number, etc., will never be disclosed to future researchers and neither will the code that links your identifiers to the sample.

In the future, people who do research may need to know more about your health. While the study investigator may give reports about your health, he/she will NOT be given your name, address, phone number, or any other identifying information about who you are, unless you agree to be contacted in the future.

____YES you many contact for future research studies
____NO I do not want to be contacted regarding future research studies.

HOW LONG WILL I BE IN THE STUDY?

You will be in the study for about 3 to 4 months. Because pregnancy is an outcome of this study, we will use information in the SART database to document the outcome of your pregnancy up until the time of delivery.

You can stop participating at any time. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences.

WHAT ARE THE RISKS OF THE STUDY?

Being in this study involves some risk to you. You should discuss the risk of being in this study with the study staff. Risks and side effects related to the procedures and drugs we are studying include:

Most commons side effects of elagolix:

- Headache
- Feeling sick to one's stomach (nausea)
- Hot flashes

Less common side effects

- Dizziness or light headed
- Diarrhea
- Changes in mood including depression
- Acne

- Migraine headaches
- Vaginal bleeding
- Tiredness or fatigue
- Hair loss
- Difficulty sleeping
- Vomiting
- Changes in sexual desire
- Swelling or bloating
- Ovarian cysts

Most common side effects of birth control pills (OCPs)

- Nausea
- Bloating
- Vaginal bleeding or spotting
- Migraine headaches
- Changes in mood or sexual desire

Vaginal bleeding
Excessive vaginal bleeding has sometimes occurred with either of the proposed treatments. Bleeding that becomes excessive, unexpected or unrelenting while on therapy may lead to withdrawal from the study and the request to stop treatment with that medication. Subjects that experience such events leading to withdrawal from the study, will be offered treatment with the alternative treatment arm for 2 more months and outcomes followed in an observational arm of the study.

Bone mineral density and risk of fracture
While long term use of elagolix at the higher dose was associated with some bone loss and potential risk of fracture, previous studies show that this risk is small for short term use as in this study.

Effects on Lipids
Long term use of elagolix has been shown to adversely affect lipid profiles, but for short term use this is unlikely to occur.

Allergic Reactions
There is always a possibility of an allergic reaction to any medication. Some cases of allergic reaction include rash, have been reported in women taking elagolix. Some people who experienced these reactions required treatment and, in some cases, stopped the study drug.

Depression or suicidal thoughts
Although uncommon, some women on estrogen lowering drugs may have mood changes that could become serious over time. After starting the treatments, the study personnel will be asking you if you are experiencing any sad thoughts or thoughts related to self-harm. Questionnaires to

evaluate the severity of any mood changes could be administered and some subjects may need to be withdrawn from the study if those mood changes are interfering with your personal safety. As part of this study, you will be asked questions about your mood while on this medication. If we learn that you or someone else is in danger of harm, the study team is required to report that information to the proper authorities.

In addition, there is a slight risk of a breach of confidentiality. We will do our best to protect your confidential information. There also may be other risks that we cannot predict. You should tell the research staff about all the medications, vitamins and supplements you take and any medical conditions you have. This may help avoid side effects, interactions and other risks.

Taking part in this research study may involve providing information that you consider confidential or private. Efforts, such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep your information safe.

A Data Safety and Monitoring Committee, an independent group of experts, will be reviewing the data from this research throughout the study.

You may experience discomfort, bruising and/or bleeding where the needle is inserted. Occasionally some people become dizzy lightheaded or feel faint. Infection may occur on rare occasions. Frequent donation of blood can result in low iron in your blood (iron deficient anemia).

Reproductive Risks and other Issues to Participating in Research

Due to unknown risks and potential harm to the unborn fetus, sexually active women of childbearing potential must use a reliable method of birth control while participating in this study. Reliable methods of birth control are: abstinence (not having sex), tubal ligation, or vasectomy of the partner (with confirmed negative sperm counts) in a monogamous relationship (same partner). An acceptable, although less reliable, method involves the careful use of condoms and spermicidal foam or gel and/or a diaphragm with spermicide with Plan B used for any noticed condom or diaphragm failures. We encourage you to discuss this issue further with your physicians if you have any questions.

Pregnant women are excluded from participation in this study. Because NO method of birth control is 100% reliable, a pregnancy test is required at least 10 days from your last normal menstrual period, if you are a sexually active woman of childbearing potential.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may be direct benefit to you. We hope the information learned from this study will benefit other people in the future. The benefits of participating in this study may be: You may have an improved chance at getting pregnant by participating in this study. Because endometriosis suppression has been shown to improve

pregnancy rates in other studies, both treatment arms may offer benefit to you. Because individuals respond differently to therapy, no one can know in advance if it will be helpful in your particular case.

WHAT OTHER CHOICES ARE THERE?

You do not have to be in this study to receive treatment. You should talk to your doctor about all the choices you have. Instead of being in this study, you have these options:
You can also agree to be part of this study without undergoing randomization, but allowing the study team to follow your outcomes after FET without further treatment. This is a valuable way to help advance our understanding of endometriosis and its effect on fertility. You can decline participation in the study and continue with your fertility treatments.

WHAT ARE THE COSTS?

All study costs, including any study medications and procedures related directly to the study, will be paid for by the study. Costs for your regular medical care, which are not related to this study, will be your own responsibility.

WILL YOUR RESEARCH RECORDS BE CONFIDENTIAL?

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed unless it is authorized by you, required by law, or necessary to protect the safety of yourself or others. There is always some risk that even de-identified information might be re-identified.

Participant information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

The purpose of this research study is to obtain data or information on the safety and effectiveness of elagolix; the results will be provided to the sponsor, the Food and Drug Administration and other federal and regulatory agencies as required.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the NIH which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

WILL YOU BE PAID FOR PARTICIPATING?

You will receive no payment or other compensation for taking part in this study.

The findings from this research may result in the future development of products that are of commercial value. There are no plans to provide you with financial compensation or for you to share in any profits if this should occur.

WHO IS SPONSORING THIS STUDY?

This study is being sponsored by the NIH. The sponsor is providing money or other support to Wake Forest University Health Sciences to help conduct this study. Elagolix, the drug under study, is manufactured by AbbVie. The Principal Investigator, Dr. Bruce Lessey, is a scientific advisor for AbbVie and has received compensation from AbbVie for consulting services related to the development of elagolix. Dr. Lessey also has a financial interest in the biomarkers being used in the research. This means that the results of this study could lead to personal profit for the investigator if the biomarkers are licensed for use related to this research.

WHAT HAPPENS IF YOU EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THIS STUDY?

Should you experience a physical injury or illness as a direct result of your participation in this study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. Wake Forest University Baptist Medical Center holds the insurance policy for this coverage. It provides a maximum of $25,000 coverage for each claim and is limited to a total of $250,000 for all claims in any one year. The Wake Forest University School of Medicine, and the North Carolina Baptist Hospitals, Incorporated do not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center's Director of Risk and Insurance Management, at [redacted].

If you are injured, the insurer may require information such as your name, social security

number, and date of birth in order to pay for your care. This is because the insurer is required by law to report any payments made to cover the care of any persons who are members of a government insurance plan to the Department of Health and Human Services.

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call *Bruce A Lessey MD, PhD, at* [redacted].

WHAT ABOUT MY HEALTH INFORMATION?

In this research study, any new information about your health or behaviors is considered Protected Health Information. The information we will collect for this research study includes**:**

- Age
- Weight and height
- Pregnancy history
- Infertility diagnosis
- Prior medical records about infertility treatments
- Hormone levels during FET
- Details regarding embryos and transfer
- Pregnancy outcomes

We will make every effort to keep your Protected Health Information private. We will store records of your Protected Health Information in a cabinet in a locked office or on a password protected computer.

Your personal health information and information that identifies you ("your health information") may be given to others during and after the study. This is for reasons such as to carry out the study, to determine the results of the study, to make sure the study is being done correctly, to provide required reports and to get approval for new products.

Some of the people, agencies and businesses that may receive and use your health information are the research sponsor; representatives of the sponsor assisting with the research; investigators at other sites who are assisting with the research; central laboratories, reading centers or analysis centers; the Institutional Review Board; representatives of Wake Forest University Health Sciences and North Carolina Baptist Hospital; representatives from government agencies such as the Food and Drug Administration (FDA) or the Office of Human Research Protections (OHRP), the Department of Health and Human Services (DHHS) and similar agencies in other countries.

Some of these people, agencies and businesses may further disclose your health information. If disclosed by them, your health information may no longer be covered by federal or state privacy regulations. Your health information may be disclosed if required by law. Your health information may be used to create information that does not directly identify you. This

information may be used by other researchers. You will not be directly identified in any publication or presentation that may result from this study unless there are photographs or recorded media which are identifiable.

If required by law or court order, we might also have to share your Protected Health Information with a judge, law enforcement officer, government agencies, or others. If your Protected Health Information is shared with any of these groups it may no longer be protected by federal or state privacy rules.

Any Protected Health Information collected from you in this study that is maintained in the research records and will be kept for at least six years after the study is finished. At that time any research information not already in your medical record will either be destroyed or it will be de-identified.

You can tell Dr. Bruce Lessey that you want to take away your permission to use and share your Protected Health Information at any time by sending a letter to this address:

Bruce A Lessey MD, PhD
[redacted]

However, if you take away permission to use your Protected Health Information you will not be able to be in the study any longer. We will stop collecting any more information about you, but any information we have already collected can still be used for the purposes of the research study.

By signing this form you give us permission to use your Protected Health Information for this study.

If you choose to participate in this study, your medical record at Wake Forest University Baptist Medical Center will indicate that you are enrolled in a clinical trial. Information about the research and any medications or devices you are being given as a participant may also be included in your medical record. This part of the medical record will only be available to people who have authorized access to your medical record. If you are not a patient at this Medical Center, a medical record will be created for you anyway to ensure that this important information is available to doctors in case of an emergency.

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

A North Carolina Baptist Hospital (NCBH) medical record will be created for all study participants. Information about your participation in the study will be placed in the NCBH

medical record, along with any routine medical test results that were obtained at NCBH as part of this study.

WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. The investigators also have the right to stop your participation in the study at any time. This could be because you were not able or willing to undergo a frozen embryo transfer or if you were non-compliant in taking the study medications. Information that identifies you may be removed from the data or specimens that are collected as part of this study and could be used for future research or shared with others without additional consent. You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or in the event of a research-related injury, contact the study investigator, **Bruce A Lessey MD, PhD at** [redacted]

The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, or you would like to discuss problems or concerns, have questions or want to offer input, or you want to obtain additional information, you should contact the Chairman of the IRB at [redacted] or the Research Subject Advocate at [redacted]. You will be given a copy of this signed consent form.

SIGNATURES

I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to ask questions about being in this study and have those questions answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

For this study, I agree to be randomized to the treatment arms Yes_____ No_____
_____(Initial)

Subject Name (Printed):_____

Subject Signature: _____ Date: _____Time:_____ am pm

Person Obtaining Consent (Printed):_____

Person Obtaining Consent:_____ Date:_____ Time:_____ am pm