Kisspeptin Physiology in Patients with Hyperprolactinemia

NCT02956447

Intravenous Kisspeptin Arm Consent Form

12/30/2020

Partners HealthCare System
Research Consent Form

Subject Identification

General Template
Version Date: August 2016

Protocol Title: Kisspeptin Physiology in Patients with Hyperprolactinemia

Principal Investigator: Stephanie Seminara, MD

Site Principal Investigator:

Description of Subject Population: Adult women age 18-45 with hyperprolactinemia

For Cohort group 1: Participants who will help us study gonadotropin secretion

About this consent form

Please read this form carefully. It tells you important information about a research study. A member of our research team will also talk to you about taking part in this research study. People who agree to take part in research studies are called "subjects." This term will be used throughout this consent form.

Partners HealthCare System is made up of Partners hospitals, health care providers, and researchers. In the rest of this consent form, we refer to the Partners system simply as "Partners."

If you have any questions about the research or about this form, please ask us. Taking part in this research study is up to you. If you decide to take part in this research study, you must sign this form to show that you want to take part. We will give you a signed copy of this form to keep.

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.

Why is this research study being done?

We are doing this research study to learn how a chemical called kisspeptin (pronounced "kiss-pep-tin") can be used in the treatment of hyperprolactinemia (higher than normal prolactin levels). We want to know how it controls the reproductive system in women with this condition, and what effect kisspeptin has on their reproductive hormone levels

Reproductive hormones are chemicals the body makes naturally. A person needs a certain amount of reproductive hormones to be able to become pregnant.

Kisspeptin is a chemical that is naturally made in the body. It is involved in reproduction, and is made in very high levels in women during pregnancy.

Some studies in humans have shown that taking kisspeptin as a medication causes the body to produce hormones called gonadotropins (pronounced "go-nad-oh-trope-ins"). Gonadotropins travel through the body in the bloodstream. In women, they stimulate the ovaries to release an egg. As part of the study, you will also receive a hormone called GnRH (short for "gonadotropin-releasing hormone"). GnRH stimulates the pituitary gland to produce gonadotropins and will be given to you to make sure your body is able to respond fully to kisspeptin.

Neither kisspeptin nor GnRH is approved by the U.S. Food and Drug Administration (FDA) as a drug to treat hyperprolactinemia but we have received permission from the FDA to use these investigational chemicals as part of this research study.

We are asking you to take part in this study because you have been diagnosed with hyperprolactinemia and are between the ages of 18 and 45.

About 60 women will take part in this research study at the Massachusetts General Hospital (MGH).

Over 100 healthy volunteers taking part in research studies have received kisspeptin so far. No adverse effects related to kisspeptin have been observed. GnRH has been given to thousands of subjects and patients, and only one adverse effect has been reported. This was an allergic reaction, and it was not clear whether this reaction was related to GnRH.

The Massachusetts General Hospital is paying for this research to be done.

How long will I take part in this research study?

You will complete one screening visit and three study visits. We may schedule additional blood draws to repeat some of the lab tests done at screening. The amount of time you spend on the study will depend on your availability to schedule the visits. However, we do not expect it will take more than 6 months.

What will happen in this research study?

Screening Visit (about 1 hour)
For the screening visit you will come to the outpatient clinic of the MGH Reproductive Endocrine Unit for your initial evaluation. At this visit, we will:

- go over the study and ask you to sign this consent form,
- ask you about your health and medical history,
- give you a physical exam
- draw blood to measure your blood count, hormones, and to make sure you are generally healthy (may be conducted at the MGH Clinical Research Center).

Women who can become pregnant will also have a pregnancy test at this visit.

You will be asked **NOT** to take any **oral contraceptives,** throughout the entire time that you are enrolled in the study. If you are currently taking a dopamine agonist such as cabergoline or bromocriptine, we will ask you to stop taking it for at least 6±2 weeks before any visit with frequent blood sampling.

You may be asked to repeat some of the tests drawn at the screening visit to determine the phase of your menstrual cycle prior to your admissions to the Clinical Research Center.

Visit 1: 1st admission to the MGH Clinical Research Center (The visit will take about 13 hours to complete.)
If your screening results tell us that you qualify for the study, you will return to the hospital to be admited for Visit 1. This visit will take place up to 2 months from the screening visit depending on your availability.

We will begin this study visit by giving you a urine pregnancy test to make sure you are not pregnant. If you are not pregnant, we will place a thin, plastic tube called an intravenous line (IV) in your arm. The IV allows us to take many blood samples without having to use a needle each time.

Through the IV, we will draw a small amount of blood every 10 minutes for 12 hours to measure your hormones, including the gonadotropins (luteinizing hormone [LH] and follicle stimulating hormone [FSH]), estrogen, prolactin, and others. The IV will stay in your vein for the whole study visit.

After the last blood draw we will remove the IV line, and you can go home.

We will call you within 48 hours after you leave the Clinical Research Center to check if there are any problems, and to see if you have any questions or concerns.

Visit 2: 2nd admission to the MGH Clinical Research Center (The visit will take about 13 hours to complete.)
This study visit will take place within 22 days from Visit 1.

We will begin this study visit by giving you a urine pregnancy test to make sure you are not pregnant. If you are not pregnant, we will place the IV in your arm.

Through the IV, we will draw a small amount of blood every 10 minutes for 12 hours to measure your hormones, including the gonadotropins (luteinizing hormone [LH] and follicle stimulating hormone [FSH]), estrogen, prolactin, and others. The IV will stay in your vein for the whole study visit.

We will give you 1 dose of kisspeptin every hour starting at hour 1 and ending at hour 10 of the study. This means you will receive a total of 10 kisspeptin doses in total. We will give you one dose of GnRH at hour 11 of the study. The doses will be given to you through the IV that is already in your arm. After the last blood draw we will remove the IV line, and you can go home.

We will call you within 48 hours after you leave the Clinical Research Center to check if there are any problems, and to see if you have any questions or concerns.

Visit 3: Follow-up visit (about 30 minutes)
Within a month after Visit 2, you will return for a short physical exam. During this visit we will also collect follow-up labs to make sure your lab values are in the study eligibility range. If any of your lab values are outside of this range, we will keep you in the study until your values have returned to normal. If your blood count is low, we will give you a 1 month supply of iron pills.

You need to tell us if you have taken part in, or plan to take part in, any other research study while you are in this study. Also, please let us know about any medical, diagnostic, or treatment activites, such as a new medicine or a trip to the doctor, during this study. This is for your safety.

Stopping the Study Early

You may decide to stop taking part in the study for any reason. Also, the study doctor may take you out of the study without your permission. This may happen because:

- The study doctor thinks it is best for you to stop taking the study drug
- The study doctor thinks it is best for you to stop participating in the study

- You can't make the required study visits
- We stop doing the study for other reasons

If this happens, the study doctor will explain why you need to stop taking part in the study. We will ask you to come in for a final study visit as described above.

Review of Medical Records from Hospital Admissions or Emergency Department Visits
Partners has an electronic system that lets your study doctors know if you are admitted to a Partners Hospital, or if you visit a Partners Hospital Emergency Department. We want to make sure the study doctors know about any possible problems or side effects you experience while you are taking part in the study.

Storing Samples and Health Information at MGH for Future Use
We would like to store some of your samples and health information for future research related to reproductive disorders or kisspeptin physiology/safety. We will label your samples and health information with a code instead of your name. The key to the code connects your name to your samples and health information. The study doctor will keep the key to the code in a [password protected computer/locked file].

Do you agree to let us store your samples and health information for future research related to reproductive disorders or kisspeptin physiology/safety?

☐ Yes ☐ No Initials_____

If later you change your mind and want your samples destroyed, contact the study doctor.

Use of your Information from this Research Study

In the past you may have participated in a study in the Reproductive Endocrine Unit including providing a blood sample, spending a night in the hospital, or receiving medication/treatment. All study information, past and future including genetic studies will be used collectively for ongoing research and to improve our understanding of reproductive disorders. This includes information from other Reproductive Endocrine Unit studies you have completed or will take part in.

As we learn more about your condition, we may want to contact you about additional studies.

Study Information Included in Your Electronic Medical Record
A notation that you are taking part in this research study may be made in your electronic medical record. Information from the research that relates to your general medical care may be included in the record (for example, list of allergies, results of standard blood tests done at the hospital labs).

Please ask your study doctor if you have any questions about what information will be included in your electronic medical record.

What are the risks and possible discomforts from being in this research study?

The risks involved with this study include:

Risk of Allergic Reaction:
With any drug, an allergic reaction can occur. Allergic reactions can be mild or more serious and can even result in death. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or trouble breathing. If you think you are having an allergic reaction, call the study doctor right away. If you are having trouble breathing, call 911 immediately.

Risks of Kisspeptin:
Kisspeptin is naturally made in the human body. This drug has been given to healthy men and women, patients attempting fertility and patients with reproductive disorders. We also studied the effects of high doses of kisspeptin on rats and dogs and no side effects were seen. There have been no serious side effects seen in either animal or human studies. However, there may be risks of kisspeptin that are currently unknown, including side effects that may happen when taking kisspeptin with other drugs.

For your safety during this study, call your study doctor BEFORE you take any:

- new medications prescribed by your own doctor
- other medications sold over-the-counter without a prescription
- dietary or herbal supplements

Risks to an Embryo or Fetus, or to a Breastfeeding Infant
We do not believe that kisspeptin has any risk to an embryo or fetus (unborn baby in the womb). This is largely based on studies showing very high levels during pregnancy. There may be harmful risks that are unknown. Therefore, women cannot take part in the study if they are:

- pregnant
- breastfeeding
- trying to become pregnant

If you have had any well-documented method of surgical sterilization, you will not need to have a pregnancy test. Some methods of surgical sterilization include having had a hysterectomy

(removal of the uterus), a tubal ligation (having your tubes tied), and transvaginal occlusion (plugging the opening of the tubes with a coil). If none of these apply to you, you must have a negative pregnancy test before starting the study drug.

If you are sexually active and able to become pregnant, you must agree to use two of the birth control methods listed below. You must use two forms of birth control for the entire study and for one month after your last dose of study drug.

Acceptable birth control methods for use in this study are:

- barrier methods (such as a condom or diaphragm) used with a spermicide (a foam, cream, or gel that kills sperm)
- intrauterine device (IUD)
- abstinence (no sex)

The study investigator will discuss your choices for birth control during the study.

If you think you might be pregnant during the study, you must tell the study doctor. If you become pregnant, you must stop taking the study drug and stop taking part in the study. The study doctor may ask for your permission to collect information about the outcome of your pregnancy and the condition of your newborn.

Risks of Gonadotropin-Releasing Hormone (GnRH)

GnRH has been given to patients for more than 30 years and it is approved by the FDA for ovulation induction in women. There have been no serious side effects that were felt to be related to GnRH in human studies aside from a single report of a possible allergic reaction.

Risks of Blood Draws and IV Lines:

The total amount of blood drawn in this study is less than 2 cups. By comparison, the Red Cross allows a healthy adult to donate 1 unit (about 2 cups) of blood every 8 weeks. A healthy person will normally replace this amount of blood in that time period.

You should not donate blood or have large amounts of blood drawn for 8 weeks after the study.

You may have a bruise (a black and blue mark) or pain where we take the blood samples and/or put in an IV line. There is also a small risk of infection, lightheadedness, and/or fainting, as well as a slight chance that an IV line may stop working. If an IV line stops working, we will put in a new one. Also, it is possible that you could develop anemia from blood-drawing, should this happen we will provide iron supplements. You may feel fatigued after blood-drawing.

Risks of Iron Supplements

Iron supplements may occasionally cause mild gastrointestinal (stomach and digestion) problems, including constipation and darkening of the stool.

Dopamine Agonist Treatment Washout
If you take a dopamine agonist such as cabergoline or bromocriptine and you stop taking it, you may notice that your original symptoms may come back. These symptoms may include a lack of menstrual period, sexual dysfunction, and/or a milky liquid coming out of your breast(s) (galactorrhea). However, because our washout period is relatively short, we do not expect you to have these symptoms for very long and expect any short-term symptoms to quickly go away when you begin taking cabergoline or bromocriptine again.

Unknown Risks
There may be other risks of kisspeptin and GnRH that are currently unknown.

What are the possible benefits from being in this research study?
You will not directly benefit from taking part in this research study.

What other treatments or procedures are available for my condition?
You do not have to take part in this research study to be treated for hyperprolactinemia. Other treatments that are available to treat hyperprolactinemia include dopamine agonist therapy with bromocriptine or cabergoline.

Can I still get medical care within Partners if I don't take part in this research study, or if I stop taking part?

Yes. Your decision won't change the medical care you get within Partners now or in the future. There will be no penalty, and you won't lose any benefits you receive now or have a right to receive.

Taking part in this research study is up to you. You can decide not to take part. If you decide to take part now, you can change your mind and drop out later. We will tell you if we learn new information that could make you change your mind about taking part in this research study.

What should I do if I want to stop taking part in the study?

If you take part in this research study, and want to drop out, you should tell us. We will make sure that you stop the study safely. We will also talk to you about follow-up care, if needed.

Also, it is possible that we will have to ask you to drop out of the study before you finish it. If this happens, we will tell you why. We will also help arrange other care for you, if needed.

Will I be paid to take part in this research study?

Group 1 will receive up to $1000 for completing the study.

Screening visit: $20
Visit 1 (CRC Visit 1): $480 ($260 at time of visit; $220 at end of study).
Visit 2 (CRC Visit 2): $480 ($260 at time of visit; $220 at end of study).
Visit 3 (Follow-up Visit): $20

We will give you meals during the Clinical Research Center admissions. We will give you a parking coupon to pay for your parking in the hospital garage during study visits. If you are traveling from a distance, we may also defray transportation and hotel costs.

If there is an extra follow-up visit because you have a problem during the study, we will not pay you for the extra follow-up visit.

What will I have to pay for if I take part in this research study?

Study funds will pay for study-related items and services. We may bill your health insurer for, among other things, routine items and services you would have received even if you did not take part in the research. You will be responsible for payment of any deductibles and co-payments required by your insurer for this routine care or other billed care. If you have any questions about costs to you that may result from taking part in the research, please speak with the study doctors and study staff. If necessary, we will arrange for you to speak with someone in Patient Financial Services about these costs.

What happens if I am injured as a result of taking part in this research study?

We will offer you the care needed to treat any injury that directly results from taking part in this research study. We reserve the right to bill your insurance company or other third parties, if appropriate, for the care you get for the injury. We will try to have these costs paid for, but you may be responsible for some of them. For example, if the care is billed to your insurer, you will be responsible for payment of any deductibles and co-payments required by your insurer.

Injuries sometimes happen in research even when no one is at fault. There are no plans to pay you or give you other compensation for an injury, should one occur. However, you are not giving up any of your legal rights by signing this form.

If you think you have been injured or have experienced a medical problem as a result of taking part in this research study, tell the person in charge of this study as soon as possible. The researcher's name and phone number are listed in the next section of this consent form.

If I have questions or concerns about this research study, whom can I call?

You can call us with your questions or concerns. Our telephone numbers are listed below. Ask questions as often as you want.

Stephanie Seminara, M.D. is the person in charge of this research study. You can call her at [redacted] (Monday-Friday 9-5) or page her (# [redacted]) 24 hours a day, 7 days a week with questions about this research study. You can also call Margaret Lippincott, M.D. at [redacted] (Monday-Friday 9-5) or page her (6[redacted] pager # [redacted]) 24 hours a day, 7 days a week with questions about this research study.

If you have questions about the scheduling of appointments or study visits, call [redacted] or email mghkisspeptinresearch@partners.org.

If you want to speak with someone **not** directly involved in this research study, please contact the Partners Human Research Committee office. You can call them at 857-282-1900.

You can talk to them about:

- Your rights as a research subject
- Your concerns about the research
- A complaint about the research

Also, if you feel pressured to take part in this research study, or to continue with it, they want to know and can help.

If I take part in this research study, how will you protect my privacy?

During this research, identifiable information about your health will be collected. In the rest of this section, we refer to this information simply as "health information." In general, under federal law, health information is private. However, there are exceptions to this rule, and you

should know who may be able to see, use, and share your health information for research and why they may need to do so.

In this study, we may collect health information about you from:

- Past, present, and future medical records
- Research procedures, including research office visits, tests, interviews, and questionnaires

Who may see, use, and share your identifiable health information and why they may need to do so:

- Partners research staff involved in this study
- The sponsor(s) of this study, and the people or groups it hires to help perform this research
- Other researchers and medical centers that are part of this study and their ethics boards
- A group that oversees the data (study information) and safety of this research
- Non-research staff within Partners who need this information to do their jobs (such as for treatment, payment (billing), or health care operations)
- The Partners ethics board that oversees the research and the Partners research quality improvement programs.
- People from organizations that provide independent accreditation and oversight of hospitals and research
- People or groups that we hire to do work for us, such as data storage companies, insurers, and lawyers
- Federal and state agencies (such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health, and other US or foreign government bodies that oversee or review research)
- Public health and safety authorities (for example, if we learn information that could mean harm to you or others, we may need to report this, as required by law)
- Other: researchers and medical centers that may do similar research in the future.

Some people or groups who get your health information might not have to follow the same privacy rules that we follow and might use or share your health information without your permission in ways that are not described in this form. For example, we understand that the sponsor of this study may use your health information to perform additional research on various products or conditions, to obtain regulatory approval of its products, to propose new products, and to oversee and improve its products' performance. We share your health information only when we must, and we ask anyone who receives it from us to take measures to protect your

privacy. The sponsor has agreed that it will not contact you without your permission and will not use or share your information for any mailing or marketing list. However, once your information is shared outside Partners, we cannot control all the ways that others use or share it and cannot promise that it will remain private.

Because research is an ongoing process, we cannot give you an exact date when we will either destroy or stop using or sharing your health information.

The results of this research study may be published in a medical book or journal, or used to teach others. However, your name or other identifying information **will not** be used for these purposes without your specific permission.

Your Privacy Rights

You have the right **not** to sign this form that allows us to use and share your health information for research; however, if you don't sign it, you can't take part in this research study.

You have the right to withdraw your permission for us to use or share your health information for this research study. If you want to withdraw your permission, you must notify the person in charge of this research study in writing. Once permission is withdrawn, you cannot continue to take part in the study.

If you withdraw your permission, we will not be able to take back information that has already been used or shared with others.

You have the right to see and get a copy of your health information that is used or shared for treatment or for payment. To ask for this information, please contact the person in charge of this research study. You may only get such information after the research is finished.

Informed Consent and Authorization

Statement of Person Giving Informed Consent and Authorization

- I have read this consent form.
- This research study has been explained to me, including risks and possible benefits (if any), other possible treatments or procedures, and other important things about the study.
- I have had the opportunity to ask questions.
- I understand the information given to me.

Signature of Subject:

I give my consent to take part in this research study and agree to allow my health information to be used and shared as described above.

Subject	Date	Time (optional)

Signature of Study Doctor or Person Obtaining Consent:

Statement of Study Doctor or Person Obtaining Consent

- I have explained the research to the study subject.
- I have answered all questions about this research study to the best of my ability.

Study Doctor or Person Obtaining Consent	Date	Time (optional)

Consent of Non-English Speaking Subjects Using the "Short Form" in the Subject's Spoken Language

Statement of Hospital Medical Interpreter

As someone who understands both English and the language spoken by the subject, I interpreted, in the subject's language, the researcher's presentation of the English consent form. The subject was given the opportunity to ask questions.

Hospital Medical Interpreter	Date	Time (optional)

OR

Statement of Other Individual (Non-Interpreter)

As someone who understands both English and the language spoken by the subject, I represent that the English version of the consent form was presented orally to the subject in the subject's own language, and that the subject was given the opportunity to ask questions.

Name	Date	Time (optional)

Permission for Future Contact

We may want to contact you about additional studies in the future. Do you give permission for us to contact you about future studies?

☐ **YES, I give permission to be contacted about future studies.**

☐ **NO, I do NOT wish to be contacted about future studies.**

Subject	Date

Consent Form Version: 1/29/2020

Kisspeptin Physiology in Patients with Hyperprolactinemia

NCT02956447

Subcutaneous Kisspeptin Arm Consent Form

06/21/2023

Partners HealthCare System
Research Consent Form

Subject Identification

General Template
Version Date: August 2016

Protocol Title: Kisspeptin Physiology in Patients with Hyperprolactinemia

Principal Investigator: Stephanie Seminara, MD

Site Principal Investigator:

Description of Subject Population: Adult women age 18-45 with hyperprolactinemia

For Cohort group 2: Participants who will help us study Folliculogenesis-the process your body goes through to develop an egg in your ovary

About this consent form

Please read this form carefully. It tells you important information about a research study. A member of our research team will also talk to you about taking part in this research study. People who agree to take part in research studies are called "subjects." This term will be used throughout this consent form.

Partners HealthCare System is made up of Partners hospitals, health care providers, and researchers. In the rest of this consent form, we refer to the Partners system simply as "Partners."

If you have any questions about the research or about this form, please ask us. Taking part in this research study is up to you. If you decide to take part in this research study, you must sign this form to show that you want to take part. We will give you a signed copy of this form to keep.

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.

Why is this research study being done?

We are doing this research study to learn how a chemical called kisspeptin (pronounced "kiss-pep-tin") can be used in the treatment of hyperprolactinemia (higher than normal prolactin

IRB Protocol No: 2016P002281 **IRB Expiration Date: 11/29/2023**
Consent Form Valid Date: 6/21/2023 **IRB Submission: AME50**

levels). We want to know how it controls the reproductive system in women with this condition and if this drug can help these women with high prolactin levels to ovulate.

Reproductive hormones are chemicals the body makes naturally. A person needs a certain amount of reproductive hormones to be able to become pregnant.

Kisspeptin is a chemical that is naturally made in the body. It is involved in reproduction and is made in very high levels in women during pregnancy.

Some studies in humans have shown that taking kisspeptin as a medication causes the body to produce hormones called gonadotropins (pronounced "go-nad-oh-trope-ins"). Gonadotropins travel through the body in the bloodstream. In women, they stimulate the ovaries to release an egg.

Kisspeptin is not approved by the U.S. Food and Drug Administration (FDA) as a drug to treat hyperprolactinemia but we have received permission from the FDA to use this investigational chemical as part of this research study.

We are asking you to take part in this study because you have been diagnosed with hyperprolactinemia and are between the ages of 18 and 45.

About 41 women will take part in this research study at the Massachusetts General Hospital (MGH).

Over 100 healthy volunteers taking part in research studies have received kisspeptin so far. No adverse effects related to kisspeptin have been observed.

The Massachusetts General Hospital and the FDA are paying for this research to be done.

How long will I take part in this research study?

You will complete one screening visit and 8 study visits. The amount of time you spend on the study will depend on your availability to schedule the visits. However, we do not expect it will take more than 6 months.

What will happen in this research study?

All visits may take place at either the outpatient clinic of the MGH Reproductive Endocrine Unit or at the MGH Clinical Research Center.

If you sign this consent form and are currently taking a dopamine agonist, such as cabergoline or bromocriptine, we will ask you to stop taking it, starting 4 to 8 weeks prior to completing screening blood work and continuing until the end of the study. Additionally, if you are taking an oral contraceptive, we will ask you to stop taking it for the same time period. This "washout period" allows your regular medications to leave your body before we measure your hormone levels and general indicators of your health. Please discuss the washout period with your prescribing physician prior to beginning the washout. Without your regular medications, your medical condition or symptoms may get worse. If this happens, please call the study doctor at the number provided in this consent form. Your chances of becoming pregnant increase when you stop taking an oral contraceptive. As described later in this document, you will need to use alternate forms of birth control to participate in the study.

You need to tell us if you have taken part in, or plan to take part in, any other research study while you are in this study. Also, please let us know about any medical, diagnostic, or treatment activites, such as a new medicine or a trip to the doctor, during this study. This is for your safety.

Screening Visit (about 1 hour)
At this visit, we will:

- ask you about your health and medical history,
- give you a physical exam,
- draw blood to measure your blood count, hormones, and to make sure you are generally healthy

Women who can become pregnant will also have a pregnancy test at this visit.

Visit 1: Kisspeptin pump(s) placement- day 1 of kisspeptin administration (about 2.5 hours)
At this visit, you will undergo a pelvic ultrasound. If the results of the Visit 1 ultrasound indicate that you have the potential to ovulate an egg in your current menstrual cycle, we might stop your participation in the study.

We will place a pump(s) device that will give you kisspeptin subcutaneously (SC, under the skin), or intravenously (IV, inside the vein). The pump is about the size of a deck of cards, and it can be carried in your pocket or clipped to your belt. A thin, flexible tube will carry the kisspeptin from the pump(s) to your body. The pump(s) should not interfere with your daily activities. You will be asked to wear this device for 8 days.

You might be asked to wear only one pump, or you might be asked to wear two of the small pump devices at the same time. If you are asked to wear two pumps, you would have two insertion sites, one in each of two locations on your abdomen.

During this visit, we will collect up to a maximum of 10 blood samples (about two tablespoons in total). The first blood samples will be collected just before the pump(s) gives you the first dose of kisspeptin. We will then collect additional samples after the dose has been delivered. These blood samples will be used to measure LH (Luteinizing Hormone), FSH (Follicle Stimulating Hormone), estradiol (estrogen), prolactin and other hormones.

Visits 2-7: Daily blood sampling- days 2-7 of kisspeptin administration (about 2.5 hours)
We will ask you to come in every day at the same time of day for 6 days, in order to collect up to 10 blood samples over a period of up to 90 minutes. The blood samples will be used to measure LH, FSH, estradiol, prolactin and other hormones.

During Visit 3 or 4, you will undergo a pelvic ultrasound to continue monitoring your ovaries.

Visit 8: Final Visit – day 8 of kisspeptin administration (about 1.5 hours)
During Visit 8, you will undergo a pelvic ultrasound and the pump(s) will be removed. We will also repeat safety and hormone labs. If your blood count is low, we will give you a 1-month supply of iron pills.

Stopping the Study Early

You may decide to stop taking part in the study for any reason. Also, the study doctor may take you out of the study without your permission. This may happen because:

- The study doctor thinks it is best for you to stop taking the study drug
- The study doctor thinks it is best for you to stop participating in the study
- You can't make the required study visits
- We stop doing the study for other reasons

If this happens, the study doctor will explain why you need to stop taking part in the study. We will ask you to come in for a final study visit. During this visit you may undergo a pelvic ultrasound and we will collect a blood sample for safety and hormone labs.

Review of Medical Records from Hospital Admissions or Emergency Department Visits
Partners has an electronic system that lets your study doctors know if you are admitted to a Partners Hospital, or if you visit a Partners Hospital Emergency Department. We want to make sure the study doctors know about any possible problems or side effects you experience while you are taking part in the study.

Storing Samples and Health Information at MGH for Future Use

We would like to store some of your samples and health information for future research related to reproductive disorders or kisspeptin physiology/safety. We will label your samples and health information with a code instead of your name. The key to the code connects your name to your samples and health information. The study doctor will keep the key to the code in a [password protected computer/locked file].

Do you agree to let us store your samples and health information for future research related to reproductive disorders or kisspeptin physiology/safety?

☐ Yes ☐ No Initials_____

If later you change your mind and want your samples destroyed, contact the study doctor.

Use of your Information from this Research Study

In the past you may have participated in a study in the Reproductive Endocrine Unit including providing a blood sample, spending a night in the hospital, or receiving medication/treatment. All study information, past and future including genetic studies will be used collectively for ongoing research and to improve our understanding of reproductive disorders. This includes information from other Reproductive Endocrine Unit studies you have completed or will take part in.

As we learn more about your condition, we may want to contact you about additional studies.

Study Information Included in Your Electronic Medical Record

A notation that you are taking part in this research study may be made in your electronic medical record. Information from the research that relates to your general medical care may be included in the record (for example, list of allergies, results of standard blood tests done at the hospital labs).

Please ask your study doctor if you have any questions about what information will be included in your electronic medical record.

What are the risks and possible discomforts from being in this research study?

The risks involved with this study include:

Risk of Allergic Reaction:

With any drug, an allergic reaction can occur. Allergic reactions can be mild or more serious and can even result in death. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or trouble breathing. If you think you are

having an allergic reaction, call the study doctor right away. If you are having trouble breathing, call 911 immediately.

Risks of Kisspeptin:
Kisspeptin is naturally made in the human body. This drug has been given to healthy men and women, patients attempting fertility and patients with reproductive disorders. We also studied the effects of high doses of kisspeptin on rats and dogs and no side effects were seen. There have been no serious side effects seen in either animal or human studies. However, there may be risks of kisspeptin that are currently unknown, including side effects that may happen when taking kisspeptin with other drugs.

For your safety during this study, call your study doctor BEFORE you take any:
- new medications prescribed by your own doctor
- other medications sold over-the-counter without a prescription
- dietary or herbal supplements

Risks to an Embryo or Fetus, or to a Breastfeeding Infant
We do not believe that kisspeptin has any risk to an embryo or fetus (unborn baby in the womb). This is largely based on studies showing very high levels during pregnancy. There may be harmful risks that are unknown. Therefore, women cannot take part in the study if they are:
- pregnant
- breastfeeding
- trying to become pregnant

If you have had any well-documented method of surgical sterilization, you will not need to have a pregnancy test. Some methods of surgical sterilization include having had a hysterectomy (removal of the uterus), a tubal ligation (having your tubes tied), and transvaginal occlusion (plugging the opening of the tubes with a coil). If none of these apply to you, you must have a negative pregnancy test before starting the study drug.

If you are sexually active and able to become pregnant, you must agree to use two of the birth control methods listed below. You must use two forms of birth control for the entire study and for one month after your last dose of study drug.

Acceptable birth control methods for use in this study are:
- barrier methods (such as a condom or diaphragm) used with a spermicide (a foam, cream, or gel that kills sperm)
- intrauterine device (IUD)
- abstinence (no sex)

The study investigator will discuss your choices for birth control during the study.

If you think you might be pregnant during the study, you must tell the study doctor. If you become pregnant, you must stop taking the study drug and stop taking part in the study. The study doctor may ask for your permission to collect information about the outcome of your pregnancy and the condition of your newborn.

Ultrasound

Pelvic ultrasounds will be performed. There are no known radiation risks associated with standard ultrasound procedures. The ultrasound uses sound waves to create a picture of the internal parts of your body and can be done either transvaginally or transabdominally. The exam takes about 30 minutes. The transvaginal route gives the best picture of the uterus and ovaries and is the preferred way to do the ultrasound. The transvaginal ultrasound involves the temporary insertion of a probe into the vagina to image the ovaries and uterus and may involve some mild discomfort (less than that associated with a Pap smear). If you do not want the transvaginal ultrasound, or if you have not been sexually active previously, the ultrasound will be performed through the abdominal wall, when the bladder is full. The probe is passed back and forth over the abdomen (similar to ultrasounds done for pregnant women). The transabdominal ultrasound may involve some discomfort from the pressure placed on the abdomen, as your bladder must be full to adequately visualize the pelvic organs via this method.

Risks of Blood Draws and IV and SC Administration of study drug:

The total amount of blood drawn in this study is up to about 1 cup. The Red Cross allows a healthy adult to donate 1 unit (about 2 cups) of blood every 8 weeks. A healthy person will normally replace this amount of blood in that time period.

You should not donate blood or have large amounts of blood drawn for 8 weeks after the study.

You may have a bruise (a black and blue mark) or pain where we take the blood samples and/or put in an IV line. There is also a small risk of infection, lightheadedness, and/or fainting, as well as a slight chance that an IV line may stop working. If an IV line stops working, we will put in a new one. Also, it is possible that you could develop anemia from blood-drawing. Should this happen, we will provide you with iron supplements. You may feel fatigued after blood-drawing.

There is a possibility of a reaction at the site(s) of SC study drug administration, including: pain, tenderness, warmth, itching, swelling, irritation, redness, or bruising.

Risks of Iron Supplements

Iron supplements may occasionally cause mild gastrointestinal (stomach and digestion) problems, including constipation and darkening of the stool.

Dopamine Agonist and/or Oral Contraceptive Treatment Washout

If you take a dopamine agonist such as cabergoline or bromocriptine and you stop taking it, you might notice that your original symptoms come back, to some degree. These symptoms may include a lack of menstrual period, sexual dysfunction, and/or a milky liquid coming out of your breast(s) (galactorrhea). However, because the washout period needed to participate in the study is relatively short, we do not expect you to have these symptoms for very long and expect any short-term symptoms to quickly go away when you begin taking cabergoline or bromocriptine again. If you stop taking an oral contraceptive, you might experience the return of some symptoms that the medication lessened, and the likelihood of becoming pregnant increases, unless you are abstinent or use another highly effective form of contraception. When you start taking your oral contraceptive again, if you decide to, these changes should go away quickly.

Unknown Risks

There may be other risks of kisspeptin that are currently unknown.

What are the possible benefits from being in this research study?

You will not directly benefit from taking part in this research study.

What other treatments or procedures are available for my condition?

You do not have to take part in this research study to be treated for hyperprolactinemia. Other treatments that are available to treat hyperprolactinemia include dopamine agonist therapy with bromocriptine or cabergoline.

Can I still get medical care within Partners if I don't take part in this research study, or if I stop taking part?

Yes. Your decision won't change the medical care you get within Partners now or in the future. There will be no penalty, and you won't lose any benefits you receive now or have a right to receive.

Taking part in this research study is up to you. You can decide not to take part. If you decide to take part now, you can change your mind and drop out later. We will tell you if we learn new information that could make you change your mind about taking part in this research study.

What should I do if I want to stop taking part in the study?

If you take part in this research study, and want to drop out, you should tell us. We will make sure that you stop the study safely. We will also talk to you about follow-up care, if needed.

Also, it is possible that we will have to ask you to drop out of the study before you finish it. If this happens, we will tell you why. We will also help arrange other care for you, if needed.

Will I be paid to take part in this research study?

You will receive up to $1190 for completing the study.

Screening visit: $40
Visits 1-7: $150/visit
Visit 8: $100
Follow up visit (if participation stopped early): $40

Depending on the timing of your visit, we may give you meals during your time in the Clinical Research Center. We will give you a parking coupon to pay for your parking in the hospital garage during study visits. If you are traveling from a distance, we may also defray transportation and hotel costs.

What will I have to pay for if I take part in this research study?

Study funds will pay for study-related items and services. We may bill your health insurer for, among other things, routine items and services you would have received even if you did not take part in the research. You will be responsible for payment of any deductibles and co-payments required by your insurer for this routine care or other billed care. If you have any questions about costs to you that may result from taking part in the research, please speak with the study doctors and study staff. If necessary, we will arrange for you to speak with someone in Patient Financial Services about these costs.

What happens if I am injured as a result of taking part in this research study?

We will offer you the care needed to treat any injury that directly results from taking part in this research study. We reserve the right to bill your insurance company or other third parties, if appropriate, for the care you get for the injury. We will try to have these costs paid for, but you may be responsible for some of them. For example, if the care is billed to your insurer, you will be responsible for payment of any deductibles and co-payments required by your insurer.

Injuries sometimes happen in research even when no one is at fault. There are no plans to pay you or give you other compensation for an injury, should one occur. However, you are not giving up any of your legal rights by signing this form.

If you think you have been injured or have experienced a medical problem as a result of taking part in this research study, tell the person in charge of this study as soon as possible. The researcher's name and phone number are listed in the next section of this consent form.

If I have questions or concerns about this research study, whom can I call?

You can call us with your questions or concerns. Our telephone numbers are listed below. Ask questions as often as you want.

Stephanie Seminara, M.D. is the person in charge of this research study. You can call her at [redacted] (Monday-Friday 9-5) or page her (#[redacted]) 24 hours a day, 7 days a week with questions about this research study. You can also call Margaret Lippincott, M.D. at [redacted] (Monday-Friday 9-5) or page her ([redacted] pager #[redacted]) 24 hours a day, 7 days a week with questions about this research study.

If you have questions about the scheduling of appointments or study visits, call [redacted] or email mghkisspeptinresearch@partners.org.

If you want to speak with someone **not** directly involved in this research study, please contact the Partners Human Research Committee office. You can call them at 857-282-1900.

You can talk to them about:
- Your rights as a research subject
- Your concerns about the research
- A complaint about the research

Also, if you feel pressured to take part in this research study, or to continue with it, they want to know and can help.

If I take part in this research study, how will you protect my privacy?

During this research, identifiable information about your health will be collected. In the rest of this section, we refer to this information simply as "health information." In general, under federal law, health information is private. However, there are exceptions to this rule, and you should know who may be able to see, use, and share your health information for research and why they may need to do so.

In this study, we may collect health information about you from:

- Past, present, and future medical records

- Research procedures, including research office visits, tests, interviews, and questionnaires

Who may see, use, and share your identifiable health information and why they may need to do so:

- Partners research staff involved in this study
- The sponsor(s) of this study, and the people or groups it hires to help perform this research
- Other researchers and medical centers that are part of this study and their ethics boards
- A group that oversees the data (study information) and safety of this research
- Non-research staff within Partners who need this information to do their jobs (such as for treatment, payment (billing), or health care operations)
- The Partners ethics board that oversees the research and the Partners research quality improvement programs.
- People from organizations that provide independent accreditation and oversight of hospitals and research
- People or groups that we hire to do work for us, such as data storage companies, insurers, and lawyers
- Federal and state agencies (such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health, and other US or foreign government bodies that oversee or review research)
- Public health and safety authorities (for example, if we learn information that could mean harm to you or others, we may need to report this, as required by law)
- Other: researchers and medical centers that may do similar research in the future.

Some people or groups who get your health information might not have to follow the same privacy rules that we follow and might use or share your health information without your permission in ways that are not described in this form. For example, we understand that the sponsor of this study may use your health information to perform additional research on various products or conditions, to obtain regulatory approval of its products, to propose new products, and to oversee and improve its products' performance. We share your health information only when we must, and we ask anyone who receives it from us to take measures to protect your privacy. The sponsor has agreed that it will not contact you without your permission and will not use or share your information for any mailing or marketing list. However, once your information is shared outside Partners, we cannot control all the ways that others use or share it and cannot promise that it will remain private.

Because research is an ongoing process, we cannot give you an exact date when we will either destroy or stop using or sharing your health information.

The results of this research study may be published in a medical book or journal, or used to teach others. However, your name or other identifying information **will not** be used for these purposes without your specific permission.

Your Privacy Rights

You have the right **not** to sign this form that allows us to use and share your health information for research; however, if you don't sign it, you can't take part in this research study.

You have the right to withdraw your permission for us to use or share your health information for this research study. If you want to withdraw your permission, you must notify the person in charge of this research study in writing. Once permission is withdrawn, you cannot continue to take part in the study.

If you withdraw your permission, we will not be able to take back information that has already been used or shared with others.

You have the right to see and get a copy of your health information that is used or shared for treatment or for payment. To ask for this information, please contact the person in charge of this research study. You may only get such information after the research is finished.

Informed Consent and Authorization

Statement of Person Giving Informed Consent and Authorization

- I have read this consent form.
- This research study has been explained to me, including risks and possible benefits (if any), other possible treatments or procedures, and other important things about the study.
- I have had the opportunity to ask questions.
- I understand the information given to me.

Signature of Subject:

I give my consent to take part in this research study and agree to allow my health information to be used and shared as described above.

Subject	Date	Time (optional)

Signature of Study Doctor or Person Obtaining Consent:

Statement of Study Doctor or Person Obtaining Consent

- I have explained the research to the study subject.
- I have answered all questions about this research study to the best of my ability.

Study Doctor or Person Obtaining Consent	Date	Time (optional)

Consent of Non-English Speaking Subjects Using the "Short Form" in the Subject's Spoken Language

Statement of Hospital Medical Interpreter

As someone who understands both English and the language spoken by the subject, I interpreted, in the subject's language, the researcher's presentation of the English consent form. The subject was given the opportunity to ask questions.

Hospital Medical Interpreter	Date	Time (optional)

OR

Statement of Other Individual (Non-Interpreter)

As someone who understands both English and the language spoken by the subject, I represent that the English version of the consent form was presented orally to the subject in the subject's own language, and that the subject was given the opportunity to ask questions.

Name _____ Date _____ Time (optional) _____

Permission for Future Contact

We may want to contact you about additional studies in the future. Do you give permission for us to contact you about future studies?

☐ **YES, I give permission to be contacted about future studies.**

☐ **NO, I do NOT wish to be contacted about future studies.**

Subject _____ Date _____

Consent Form Version: 6/20/2023