INFORMED CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: A Phase 2, Single Arm, Two Period Study of Sodium Cridanimod in Conjunction with Progestin Therapy in Patients with Endometrial Carcinoma

Protocol No.: VX-EC-2-02

Sponsor: Xenetic Biosciences, Inc.
99 Hayden Avenue, Suite 230
Lexington, MA 02421

NCT Number: 03077698

Institution Name: _____

Institution Address: _____

Principal Investigator: _____

Phone number: _____

INTRODUCTION

Patients with recurrent or persistent endometrial carcinoma (cancer) are being asked to participate in a clinical research study to assess the effects of the study drug Sodium Cridanimod when combined with progestin (hormone therapy).

This Informed Consent form will describe the clinical study. The study activities will be discussed with you by the doctor and staff working on this research. If you want to be part of this clinical study, you should understand the purpose, procedure, risks and benefits. Please take time to read this Informed Consent form carefully and discuss it with others if you wish. The entire process of providing you information, giving you time to discuss the clinical study with family and friends, as well as your doctors and other health care providers and then deciding whether to participate, is known as the informed consent process. Your participation in this study is completely voluntary. You may refuse to participate. You may withdraw from the study at any time. Please ask your study doctor or the study staff to explain anything in the consent form or anything about the study that you do not understand. Once you understand the study and decide that you would like to take part, you will be asked to sign this Informed Consent form. You will be given a signed copy of this form.

A total of 72 women will be asked to participate in this study, at up to 50 study sites in the United States and Europe.

You may not participate in other clinical studies at the same time as you are participating in this clinical study. If you have concerns, please discuss with your study doctor.

This is a research study to test a new investigational drug. An investigational drug is one that is not approved by the United States Food and Drug Administration (FDA). The investigational drug used in this study is Sodium Cridanimod. More than 750 subjects have received Sodium Cridanimod in clinical studies.

PURPOSE OF THIS STUDY

The purpose of this study is to compare the effects of using Sodium Cridanimod in combination with the progestin, megestrol acetate (hormone therapy). Progestin is a synthetically produced hormone while progesterone is the natural hormone the body produces.

Hormone therapy has shown some effectiveness in treating certain endometrial cancers where the tumor tissue has receptors for progesterone. Receptors are proteins inside the cells of the female reproductive tissue that allow progesterone or synthetic progestin to attach to the tissue. In tumors where the tissue does not have enough progesterone receptors, the hormone therapy is not as effective.

A previous study of Sodium Cridanimod added to hormone therapy, conducted in women with endometrial carcinoma, showed the progesterone receptor activity on tumor tissue was increased. In pre-clinical experiments in animals, Sodium Cridanimod both increased progesterone receptor levels and reduced tumor size. The addition of the study drug Sodium Cridanimod to the hormone therapy could increase the level of progesterone receptors in your tumor tissue, allowing the hormone therapy to work in shrinking the tumor size. Since Sodium Cridanimod could also cause side effects, an assessment of its safety is also a purpose of the study.

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 use NCT code number 03077698 to search the Web site.

STUDY DURATION

The time you will be in the study may be up to 36 months (or longer, depending on your disease progression). The duration of your individual participation will depend upon other factors as detailed in the following sections.

OPTIONAL PK SUB-STUDY

There is an optional sub-study within this study that your study doctor will discuss with you. If interested, you will consent to this sub-study in addition to consenting to the main study. Participation in this optional sub-study is not required for you to be able to take part in the main study.

Study doctors are trying to learn more about distribution of and levels of the study drugs in the blood. This is called pharmacokinetics (PK).

An important objective of this optional sub-study is to investigate the possible PK of megestrol acetate when administered alone (Treatment Period 1), and the drug-drug interactions of Sodium Cridanimod and megestrol acetate when administered together (Treatment Period 2).

If you consent to participate in the optional PK Sub-Study, additional blood samples will be taken from you as follows:

- At 10 timepoints during Treatment Period 1: At Study Visit -3, before administration of megestrol acetate, and 1, 2, 3, 4 and 6 hours after administration. Blood samples will additionally be taken 1 day (24 hrs) later, 2 days (48 hrs) later, 3 days (72 hrs) later, and 4 days (96 hrs) later.

  Subjects who are PrR negative will not participate in the Treatment Period 1 portion of the PK Sub-Study.

- At 15 timepoints during Treatment Period 2: At Study Visit 1, before administration of the study drugs and at 15, 30, 45, 60 and 90 minutes, 2, 3, 4 and 6 hours after administration. Additionally on Days 3, 7, 10 and Visits 3 and 4 prior to the administration of both Sodium Cridanimod and megestrol acetate.

Your samples will be sent to a special laboratory for assessment. The samples will be kept until they are tested.

At the end of this Informed Consent Form is a PK Sub-Study consent section for you to complete as to whether you want to participate in this optional sub-study.

VISIT SCHEDULE AND STUDY PROCEDURES

Screening Period (within 4 weeks prior to the start of Treatment)

The following will be completed during the Screening Period:

- You will sign this Informed Consent form
- Your study doctor will
  - review your eligibility to be in the study
  - review your medical history with you
  - record all medications you are currently taking
  - discuss your overall abilities in your daily living activities with you
  - discuss side effects with you
- You will have a physical exam, including vital signs (blood pressure, heart rate and temperature), height and weight
- Blood samples will be taken for blood cell counts and for determining any elements, minerals and proteins in your blood
- A urine sample will be taken for general urinalysis
- A blood (serum) pregnancy test will be taken (for women who have the possibility of becoming pregnant)
- You will have an electrocardiogram (ECG) which is a recording of your heart rhythm
- Your archived (saved) tumor sample will be sent to a central lab to be tested for PrR Status*
- You will have an MRI or CT scan of any tumors to determine a baseline assessment (this must be done within 10 days of the start of Treatment)

*During the Screening process, a stored sample of your tumor (from when you were diagnosed or a recent biopsy) will be used to determine whether the progesterone receptors on your tumor are Progesterone (PrR) *Positive* or Progesterone (PrR) *Negative*.

- ***PrR Positive Status***
  If your tumor sample tested at Screening determines you have progesterone receptor (PrR) *positive* status, you will participate in Treatment Period 1 for up to 24 weeks and, if qualified, you will participate in Treatment Period 2.

- ***PrR Negative Status***
  If your tumor sample tested at Screening determines you have PrR *negative* status you will enroll directly into Treatment Period 2.

PrR Positive Patients Only;

Treatment Period 1 (Hormone Therapy Only) – (Time Frame: up to 24 weeks)

During Treatment Period 1, you will take an oral hormone therapy (megestrol acetate) and keep a Patient Diary of each dose.

Megestrol Acetate Therapy During Treatment Period 1:

The megestrol acetate will be dispensed to you as 40 mg tablets in 100 count bottles. Tablets are to be taken by mouth. You will take 2 tablets each morning and 2 tablets each evening. You will be issued a Patient Diary with every bottle and asked to record each dose (including doses taken in clinic during study visits). You will be responsible for returning empty bottles and completed Patient Diaries to the study staff at study visits. One bottle of megestrol acetate should be enough for 25 days before you need to open a new bottle. It is important that you keep unused study drug out of the reach of children and those of limited ability to understand and that the study drug is only taken by you, the research participant.

Visit -3 (Treatment Start)

- Your study doctor will
    - review your eligibility to be in the study
    - record all medications you are currently taking
    - discuss side effects with you
- Your vital signs will be taken
- You will have an ECG
- You will take your first dose of megestrol acetate in the clinic during this visit after the ECG (and for subjects participating in the optional PK Sub-Study, the dose must be taken as outlined below)
- You will be issued a supply of megestrol acetate to take home
- You will be issued Patient Diaries to take home to record your doses of megestrol acetate, as well as any side effects and any other medications you are taking
- **Optional PK Sub-Study Participants Only (all occurring for Visit -3):**
    - Blood samples will be taken for the PK Sub-Study at 10 timepoints:
        - Before administration of megestrol acetate
        - 1 hour, 2 hours, 3 hours, 4 hours, and 6 hours after administration of megestrol acetate

    In addition, you will need to return to the clinic for additional samples to be taken:
        - 1 day later (24 hours after megestrol acetate administration)
        - 2 days later (48 hours after megestrol acetate administration)
        - 3 days later (72 hours after megestrol acetate administration)
        - 4 days later (96 hours after megestrol acetate administration)

**** If Visit -3 occurs more than 7 days after the Screening visit, the following assessments will also be performed:***

- Physical exam, including weight
- Blood samples will be taken for blood cell counts and for determining any elements, minerals and proteins in your blood
- Your study doctor will discuss with you your overall abilities in your daily living activities

Visit -2 (6 weeks after Visit -3, ± 3 days)

- Your study doctor will
  - record all medications you are currently taking
  - discuss your overall abilities in your daily living activities with you
  - discuss side effects with you
  - discuss with you taking your megestrol acetate at home and answer any questions
- You will have a physical exam, including vital signs and weight
- Blood samples will be taken for blood cell counts and for determining any elements, minerals and proteins in your blood
- You will have an ECG
- You will be administered your dose of megestrol acetate if your dose time occurs during your visit time, and you will continue your dosing at home
- You will return any empty bottles of megestrol acetate and receive a new supply
- You will return any completed Patient Diaries and you will be issued new Patient Diaries

Visit -1 (12 weeks after Visit -3, ± 3 days)

- Your study doctor will
  - record all medications you are currently taking
  - discuss your overall abilities in your daily living activities with you
  - discuss side effects with you
  - discuss with you taking your megestrol acetate at home and answer any questions
- You will have a physical exam, including vital signs and weight
- Blood samples will be taken for blood cell counts and for determining any elements, minerals and proteins in your blood
- You will have an ECG
- You will be administered your dose of megestrol acetate if your dose time occurs during
- You will return any empty bottles of megestrol acetate and receive a new supply
- You will return any completed Patient Diaries and you will be issued new Patient Diary(ies)
- You will have an MRI or CT scan for tumor assessment
- You will continue to take the megestrol acetate while waiting for the results of the scan

The MRI or CT scan performed at Visit -1 will determine if you continue in Treatment Period 1 or if you are eligible to enter Treatment Period 2.

- If your MRI or CT scan at Visit -1 shows your disease is stable or there is a response to treatment, you will continue in Treatment Period 1, to Visit TP1-EXT.
- If your MRI or CT scan at Visit -1 shows your disease has progressed, you will be eligible to enter Treatment Period 2 (Visit 1, Day 0).

Visit TP1-EXT (24 weeks after Visit -3, ± 3 days)

- Your study doctor will
  - record all medications you are currently taking
  - discuss your overall abilities in your daily living activities with you
  - discuss side effects with you

    - discuss with you taking your megestrol acetate at home and answer any questions
- You will have a physical exam, including vital signs and weight
- Blood samples will be taken for blood cell counts and for determining any elements, minerals and proteins in your blood
- You will have an ECG
- You will be administered your dose of megestrol acetate if your dose time occurs during your visit time
- You will return any empty bottles of megestrol acetate and receive a new supply
- You will return any completed Patient Diaries and you will be issued new Patient Diary(ies)
- You will have an MRI or CT scan for tumor assessment
- You will continue to take the megestrol acetate while waiting for the results of the scan

The MRI or CT scan performed at Visit TP1-EXT will determine if you will have an End of Study Visit and exit the study or if you are eligible to enter Treatment Period 2.

- If your MRI or CT scan at Visit TP1-EXT continues to show your disease is stable or there is a response to treatment, you will return within 2 weeks for the End of Study Visit. You will continue to be treated by your primary doctor outside of the study (which can include continuation of the hormone therapy).
- If your MRI or CT scan at Visit TP1-EXT shows your disease has progressed, you will be eligible to enter Treatment Period 2 (Visit 1, Day 0).

End of Study Visit (EOS) – *For subjects withdrawing from the study in TP1 only*

For subjects that discontinue during TP1 for any reason and those assessed to have disease control at Visit TP1-EXT.

- If you decide to or are discontinued early from TP1, you should return to the clinic for the End of Study Visit as soon as you are able.
- If it is determined that you have disease control at TP1-EXT, you will need to return to the clinic for the End of Study Visit within 2 weeks of your TP1-EXT Visit date.
- You should continue taking your megestrol acetate at home and completing the diary until the End of Study Visit unless your study doctor or primary doctor determines the megestrol acetate is not the best treatment for you.

Study Procedures During the End of Study Visit:

- Your study doctor will
    - record all medications you are currently taking
    - discuss your overall abilities in your daily living activities with you
    - discuss side effects with you
    - discuss with you taking your megestrol acetate at home and answer any questions
- You will have a physical exam, including vital signs and weight
- Blood samples will be taken for blood cell counts and for determining any elements, minerals and proteins in your blood
- A urine sample will be taken for general urinalysis
- A urine sample will be taken for a Pregnancy Test (for women who have the possibility of becoming pregnant)

- You will have an ECG
- You will return all remaining bottles of megestrol acetate
- You will return all remaining completed Patient Diaries

PrR Negative Patients and Eligible Patients From TP1:

Treatment Period 2 (Combined Treatment)

For TP1 entering Treatment Period 2:

- There should be no interruption in taking megestrol acetate between Treatment Period 1 and Treatment Period 2.

During Treatment Period 2, you will receive Sodium Cridanimod by injection along with taking an oral hormone therapy (megestrol acetate) and keeping a Patient Diary of each dose.

Visit 1, Day 0 (Week 0) - (Combination Treatment Start)

- Your study doctor will
    - review your eligibility to be in the study
    - record all medications you are currently taking
    - discuss your overall abilities in your daily living activities with you
    - discuss side effects with you
    - discuss with you taking your megestrol acetate at home and answer any questions (for subjects continuing from Treatment Period 1)
- You will have a physical exam, including vital signs, height and weight
- Blood samples will be taken for blood cell counts and for determining any elements, minerals and proteins in your blood
- ECGs: You will need to stay in the clinic for additional time (6 hours +) during Study Visit 1 for ECG measurements. You will have 5 ECG recordings, once before administration of the study drugs, and then 15 minutes, 1 hour, 2 hours and 6 hours after administration of the study drugs.
- You will return any completed patient diaries and remaining megestrol acetate (Treatment Period 1 subjects)
- You will be issued a supply of megestrol acetate
- You will be issued Patient Diaries to record your doses of megestrol acetate, as well as any side effects and any other medications you are taking
- You will take your first dose of megestrol acetate in the clinic during this visit after the first ECG (and for subjects participating in the optional PK Sub-Study, the dose must be taken as outlined below).
- You will have your first administration of Sodium Cridanimod, given by injection intramuscularly. You will be monitored closely for a one-hour period by your study doctor and study staff after this first administration.

- **Optional PK Sub-Study Participants Only:**
    - ***Visit 1 (Day 0):*** Blood samples will be taken for the PK Sub-Study: before administration of Sodium Cridanimod and megestrol acetate, and 15 min, 30 min, 45 min, 60 min, 90 min, 2, 3, 4 and 6 hours after administration of Sodium Cridanimod and megestrol acetate. You will need to remain at the clinic for this additional 6 hour timeframe during this study visit.

- ***Days 3, 7 and 10:*** Blood samples will be taken on Days 3, 7 and 10 (before Sodium Cridanimod and megestrol acetate administration) for subjects taking part in the PK Sub-Study.

Study Drugs During Treatment Period 2:

- ***Sodium Cridanimod***

You will come to the clinic twice a week for Sodium Cridanimod injections, either on Schedule 1: Mondays and Thursdays or Schedule 2: Tuesdays and Fridays, as shown in the table below:

	Schedule of Sodium Cridanimod Administration						
	Monday	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**	**Sunday**
Schedule 1	X			X			
Schedule 2		X			X		

- ***Megestrol Acetate***

The megestrol acetate will be dispensed to you as 40 mg tablets in 100 count bottles. Tablets are to be taken by mouth. You will take 2 tablets each morning and 2 tablets each evening. You will be issued a Patient Diary with every bottle and asked to record each dose (including doses taken in clinic during study visits). You will be responsible for returning empty bottles and completed Patient Diaries to the study staff at study visits. One bottle of megestrol acetate should be enough for 25 days before you need to open a new bottle. It is important that you keep unused study drug out of the reach of children and those of limited ability to understand and that the study drug is only taken by you, the research participant.

Visit 2 (Week 4, ± 3 days)

- Your study doctor will
  - record all medications you are currently taking
  - discuss side effects with you
  - discuss with you taking your megestrol acetate at home and answer any questions
- Your vital signs will be taken
- Blood samples will be taken for blood cell counts and for determining any elements, minerals and proteins in your blood
- You will have an ECG
- You will return any empty bottles of megestrol acetate and receive a new supply
- You will return any completed Patient Diaries and you will be issued a new Patient Diary(ies)
- You will be administered your dose of megestrol acetate if your dose time occurs during your visit time
- You will continue to be administered Sodium Cridanimod at clinic visits 2 times per week

Visit 3 (Week 8, ± 3 days)

- Your study doctor will
  - record all medications you are currently taking
  - discuss your overall abilities in your daily living activities with you
  - discuss side effects with you
  - discuss with you taking your megestrol acetate at home and answer any questions

- You will have a physical exam, including vital signs and weight
- Blood samples will be taken for blood cell counts and for determining any elements, minerals and proteins in your blood
- ECGs: You will need to stay in the clinic for additional time (6 hours +) during Study Visit 3 for ECG measurements. You will have 5 ECG recordings, once before administration of the study drugs, and then 15 minutes, 1 hour, 2 hours and 6 hours after administration of the study drugs.
- You will return any empty bottles of megestrol acetate and receive a new supply
- You will return any completed Subject Diaries and you will be issued a new Patient Diary(ies)
- You will be administered your dose of megestrol acetate if your dose time occurs during your visit time
- You will continue to be administered Sodium Cridanimod at clinic visits 2 times per week

Optional PK Sub-Study Participants Only:

- Collection of blood samples for optional PK sub-study before administration of Sodium Cridanimod and megestrol acetate

Visit 4 (Week 12, ± 3 days)

- Your study doctor will
  - record all medications you are currently taking
  - discuss side effects with you
  - discuss with you taking your megestrol acetate at home and answer any questions
- You will have your vital signs taken
- Blood samples will be taken for blood cell counts and for determining any elements, minerals and proteins in your blood
- You will have an ECG
- You will have an MRI or CT scan for tumor assessment
- You will return any empty bottles of megestrol acetate and receive a new supply
- You will return any completed Patient Diaries and you will be issued a new Patient Diary(ies)
- You will be administered your dose of megestrol acetate if your dose time occurs during your visit time, and you will continue your dosing at home
- You will continue to be administered Sodium Cridanimod at clinic visits 2 times per week

Optional PK Sub-Study Participants Only:

- Collection of blood samples for optional PK sub-study before administration of Sodium Cridanimod and megestrol acetate

Visit 5 (Week 16, ± 3 days)

- Your study doctor will
  - record all medications you are currently taking
  - discuss your overall abilities in your daily living activities with you
  - discuss side effects with you
  - discuss with you taking your megestrol acetate at home and answer any questions
- You will have a physical exam, including vital signs and weight

- Blood samples will be taken for blood cell counts and for determining any elements, minerals and proteins in your blood
- You will have an ECG
- You will return any empty bottles of megestrol acetate and receive a new supply
- You will return any completed Patient Diaries and you will be issued a new Patient Diary(ies)
- You will be administered your dose of megestrol acetate if your dose time occurs during your visit time, and you will continue your dosing at home
- You will continue to be administered Sodium Cridanimod at clinic visits 2 times per week

Visit 6 (Week 20, ± 3 days)

Same procedures as Visit 2

Visit 7 (Week 24, ± 3 days)

- Your study doctor will
  - record all medications you are currently taking
  - discuss your overall abilities in your daily living activities with you
  - discuss side effects with you
  - discuss with you taking your megestrol acetate at home and answer any questions
- You will have a physical exam, including vital signs and weight
- Blood samples will be taken for blood cell counts and for determining any elements, minerals and proteins in your blood
- You will have an ECG
- A urine sample will be taken for general urinalysis
- A urine sample will be taken for a Pregnancy Test (for women who have the possibility of becoming pregnant)
- You will have an MRI or CT scan for tumor assessment
- You will return any empty bottles of megestrol acetate and receive a new supply
- You will return any completed Patient Diaries and you will be issued a new Patient Diary(ies)
- You will be administered your dose of megestrol acetate if your dose time coincides with your visit time, and you will continue your dosing at home
- You will continue to be administered Sodium Cridanimod at clinic visits 2 times per week

Visit 8 (Week 28, ± 3 days)

Same procedures as Visit 2

Visit 9 (Week 32, ± 3 days)

Same procedures as Visit 5

Visit 10 (Week 36, ± 3 days)

Same procedures as Visit 4 except there will not be a blood sample collection for the optional PK sub-study.

Visit 11 (Week 40, ± 3 days)
Same procedures as Visit 5

Visit 12 (Week 44, ± 3 days)
Same procedures as Visit 2

- At Visit 12, if your disease has not progressed, a three-month supply of megestrol acetate will be issued.
- After Visit 12, your regular study visits will occur every 12 weeks instead of every 4 weeks.

Visit 13 (Week 48, etc., ± 7 days) – and Every 12 Weeks Thereafter

- Your study doctor will
  - record all medications you are currently taking
  - discuss your overall abilities in your daily living activities with you
  - discuss side effects with you
  - discuss with you taking your megestrol acetate at home and answer any questions
- You will have a physical exam, including vital signs and weight
- Blood samples will be taken for blood cell counts and for determining any elements, minerals and proteins in your blood
- You will have an ECG
- A urine sample will be taken for general urinalysis
- You will have an MRI or CT scan for tumor analysis
- You will return any empty bottles of megestrol acetate and receive a new supply
- You will return any completed Patient Diaries and you will be issued a new Patient Diary(ies)
- You will be administered your dose of megestrol acetate if your dose time occurs during your visit time, and you will continue your dosing at home
- You will continue to be administered Sodium Cridanimod at clinic visits 2 times per week
- You will continue taking the megestrol acetate at home and completing Patient Diaries as long as you remain in the treatment period of the study and are receiving Sodium Cridanimod injections.

You will continue in the study unless your disease progresses. If your disease progresses (confirmed by an MRI or CT scan), you will stop treatment and enter the Follow-up Period.

Follow-up Period *[for participants in Treatment Period 2 only]*

The Follow-up Period consists of a Safety Follow-up Visit 4 weeks after stopping treatment, and an additional 12 months where your study doctor will monitor your health status for study purposes.

Safety Follow-up Visit (4 weeks after the discontinuation of Combination Treatment, ± 3 days)
[for participants in Treatment Period 2 only]

The following will be performed at the Safety Follow-up Visit:

- Your study doctor will
  - record all medications you are currently taking
  - discuss your overall abilities in your daily living activities with you

    - discuss side effects with you
- You will have a physical exam, including vital signs and weight
- Blood samples will be taken for blood cell counts and for determining any elements, minerals and proteins in your blood
- You will have an ECG
- A urine sample will be taken for general urinalysis
- A urine pregnancy test will be taken (for women who have the possibility of becoming pregnant)
- You will return any partially used or empty bottles of megestrol acetate
- You will return your Patient Diary(ies)
- You will have an MRI or CT scan for tumor assessment if you have discontinued the study treatment for a reason other than disease progression.

You will continue to be followed for an additional 12-month period after your last treatment by telephone or other contact by your study doctor.

WITHDRAWAL FROM TREATMENT

1. Your study doctor may withdraw you from treatment, including participation in the optional sub-study, when any of the following occur:
    - You decide to withdraw from treatment
    - Your disease progresses in Treatment Period 2
    - You have a side effect that the study doctor determines may be related to either of the study medications
    - You have another illness that prevents further administration of treatment
    - You have an unacceptable side effect
    - General or specific changes in your condition which render you unacceptable for further treatment in the judgment of your study doctor
    - You enter another clinical study
    - New safety information becomes available that may impact your continued participation in the trial
    - The study is stopped by the Sponsor, the IRB/IEC, or other regulatory authorities

2. You can withdraw from treatment, decide to stop participating in the study, including the optional sub-study, at any time. It is entirely up to you to decide if you want to participate or not. You should not feel obligated to participate or continue to participate.

    Possible reasons for deciding to withdraw your consent from the study, including the sub-study, are:

    - Side effects
    - Unsatisfactory therapeutic effect
    - Reason not related to treatment or study

    No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

    If you decide to stop for any reason, it is important to let your study doctor know as soon as possible so you can stop safely.

- If you decide to stop treatment during Treatment Period 1, you will need to come to the clinic within 2 weeks for the End of Study Visit.
- If you decide to stop treatment during Treatment Period 2, you will need to come to the clinic 4 weeks after stopping drug for the Safety Follow up Visit. Your study doctor will continue to monitor you for study purposes through phone call or other contact for an additional 12 months.

3. Additional Scan: If you withdraw or are withdrawn from the study during either Treatment Period 1 or Treatment Period 2, for a reason other than disease progression, an MRI or CT scan should be performed (unless a scan was done within 4 weeks of withdrawal) to determine your disease progression.

RISKS AND DISCOMFORTS

As with all medications, side effects may occur. It is important, that you report any adverse reactions to the study doctor or study staff immediately.

Possible Side Effects of Sodium Cridanimod

There have been no serious side effects reported during Sodium Cridanimod treatment. Sodium Cridanimod has been shown to be well tolerated. Following are non-serious side effects reported that were determined related to Sodium Cridanimod treatment in a total of 759 patients:

- **Very Common**

  96% of people receiving Sodium Cridanimod have experienced:

  - Burning pain at the site of injection of moderate intensity occurring immediately after injection and lasting up to 20-30 minutes. In this study Sodium Cridanimod will be injected with lidocaine to help relieve pain. It has been shown in previous clinical studies that lidocaine significantly reduces the pain associated with the Sodium Cridanimod injection.

- **Rare**

  Less than 1% of people receiving Sodium Cridanimod have experienced one or more of these:

  - Burning lips
  - Dizziness
  - Face flushing
  - Headache
  - Increased level of white blood cells
  - Sleepiness/ fatigue/ tired all the time
  - Sore throat/ pain in the back of the mouth/throat
  - Weakness

Blood Samples (main study and optional PK sub-study) and Injection

During the collection of blood samples and when Sodium Cridanimod dosage is given by injection, you may experience the following at the sites on your arm where blood is taken and where the injection occurred:

- slight discomfort
- a small amount of bleeding

- pain
- discoloration and/or bruising
- clot formation and infections may occur at the puncture site (this is extremely rare)
- fainting may occur during or shortly after having blood drawn. If you experience faintness, you should lie down immediately to avoid possible injury caused by falling. Notify the study staff.

Possible Side Effects of Megestrol Acetate

- **As listed in the current approved labeling information for megestrol acetate:**

  The following side effects are typically non-serious; if any of these persist or worsen, notify your study doctor promptly. Most people using this medication do not have serious side effects.

  - Alopecia (spot hair loss usually on the scalp)
  - Breakthrough menstrual bleeding
  - Carpal tunnel syndrome
  - Edema (swelling)
  - Gas
  - Glucose intolerance (increased risk of developing diabetes)
  - Hot flashes
  - Hyperglycemia (high blood sugar)
  - Hypertension (high blood pressure)
  - Increased appetite
  - Indigestion (heartburn)
  - Lethargy (lack of energy)
  - Malaise (general feeling of discomfort)
  - Mood changes
  - Nausea
  - Rash
  - Sweating
  - Vomiting
  - Weakness
  - Weight gain

  The following side effects are typically rare but can be serious. Seek immediate medical attention if any of these side effects occur:

  - Difficulty breathing
  - Heart failure
  - Pulmonary embolism (a blockage of the main artery of the lung or one of its branches by a thrombus (blood clot))Thrombophlebitis (vein inflammation related to a thrombus (blood clot))
  - Tumor flare

- **Use in Diabetics**: Exacerbation of preexisting diabetes with increased insulin requirements has been reported in association with the use of Megestrol acetate.

- **HPA axis suppression risk:** The megestrol acetate you will be taking in this study is an oral form of cortisone. People who take cortisone by mouth for periods of time may suppress their adrenal glands from making their own normal amounts of cortisone. This may cause little or no symptoms. In most individuals, the body will begin making its own cortisone shortly after you stop

the oral form of cortisone. However some individuals will take months, years or never begin making their own cortisone. Even without symptoms, your body may not respond to physical stress such as surgery, breaking a bone or severe illness. At these times you may require additional cortisone. You should discuss this possibility with your study doctor so that he/she will be able to watch for symptoms of not being able to cope with physical stress and provide treatment.

Possible Side Effects of Lidocaine hydrochloride

- **As listed in a current approved labeling information for Lidocaine hydrochloride:**

The following side effects are typically non-serious. Most people using this medication do not have serious side effects.

In this study, Lidocaine will always be administered with the study drug Sodium Cridanimod by an experienced doctor or nurse who will monitor how you are feeling during and after you receive the injection.

- These side effects are usually brief and do not last long, if they occur at all:
  - apprehension
  - confusion
  - dizziness/ lightheadedness
  - drowsiness
  - euphoria (a feeling of happiness and well-being)
  - fainting
  - nervousness
  - sensations of heat, cold, numbness
  - tinnitus (noise or ringing in the ears)
  - vomiting
- The following side effects are typically rare but can be serious. Immediate medical attention will be administered if any of these side effects occur:
  - cardiac arrest
  - collapse
  - convulsions
  - hypotension (low blood pressure)
  - slow/shallow breathing
  - slow/irregular heartbeat
  - seizures
  - severe confusion
  - severe drowsiness
  - severe nervousness
  - twitching
  - tremors
  - vision changes (e.g., double or blurred vision)
  - unconsciousness
- **Serious Allergic Reaction:** A very serious allergic reaction to Lidocaine is rare. However, immediate medical attention will be administered if any of these side effects occur. Please immediately notify the study staff if you notice any of the following symptoms of a serious allergic reaction:
  - difficulty breathing

- rash
- itching/swelling (especially of the face/tongue/throat)
- severe dizziness

Computed Tomography (CT) SCAN

Concerns about CT scans include the risks from exposure to ionizing radiation and possible reactions to the contrast agent. Usually CT scans of chest, abdomen and pelvis are performed with intravenous administration of a contrast agent which is like a dye and will spread through your body and will help give clearer images of your tumor. After intravenous administration of the contrast agent, you may develop a feeling of heat, occasional hot flushes, nausea, heart palpitations and/or allergic reactions. These are quite common effects of a contrast agent. Please notify the radiology team of any previous reactions to these dyes.

The computed tomograph*y* that you will receive in this study will expose you to low amounts of radiation. No one knows for sure whether exposure to low amounts of radiation is harmful for your body. However, scientists believe that being exposed to too much radiation can cause harmful side effects, including causing a new cancer.

Before the examination you should not eat anything for 4 hours before the procedure; you can only drink small amounts of water because the examination is performed on an empty stomach.

The examination will be performed with you lying down on the examination table, which is moved into an X-ray tube with sensors inside the device (also known as "the tunnel"), where you will lie for 1 to 10 minutes, until the scan is completed. A certain degree of cooperation is required during the examination (you will have to hold your breath for a few moments during the scanning process).

MRI (Magnetic Resonance Imaging)

Each MRI scan lasts approximately 40-50 minutes, during which you will be asked to lie flat in the MRI scanner. You will hear a loud tapping or thumping noise during the exam. Earplugs or earphones may be provided to you to help block the noise. The technologist will talk to you throughout the exam. During the exam you will need to remain very still. The exam is painless. You may feel warmth in the area being examined. You will at times be asked to hold your breath for a brief period of time during the scan.

During the exam, you may feel “closed in” or claustrophobic. If this is a concern, speak to your study doctor when the MRI is scheduled. Your study doctor may suggest a mild sedative to help you feel more comfortable during the MRI exam. The MRI technologist is experienced in working with people who are uncomfortable in close spaces. “Short bore” MRI machines are shorter and wider and do not totally enclose the patient. “Open” MRI machines are available for those who are unable to use a conventional MRI; however the image quality varies.

Before an MRI you will be given a hospital gown to wear or instructed to wear loose clothing without metal fasteners. You will be asked to remove all accessories, such as jewelry or hair pins/clips. Also you will be asked to remove wigs, dentures, glasses, and hearing aids. Metal objects may interfere with the magnetic field during the exam, affecting the quality of the MRI images. The magnetic field may damage electronic items. Tell the technologist (the person performing the MRI) if you have:

- any prosthetic joints
- a pacemaker, defibrillator, or artificial heart valve
- an implanted venous access device
- an intrauterine device (IUD)
- any metal plates, pins, screws, staples or bullets/shrapnel
- tattoos or permanent make-up

- a transdermal patch
- anxiety in confined spaces (claustrophobia)
- any concerns about being pregnant (for women who have the possibility of becoming pregnant)

Reproductive Risks (for women who have the possibility of becoming pregnant)
You should not get pregnant or breastfeed while in this study. The therapy used in this study could be very damaging to an unborn baby. This study requires women who have the possibility of becoming pregnant to use barrier methods of contraception during the study and during 3 months after stopping the research drugs. Barrier methods can include: diaphragm, IUD, cervical cap, cervical shield, male condom, female condom and spermicidal foam, sponges, and film. Check with your study doctor about what types of birth control, or pregnancy prevention, to use while in this study. Oral contraceptives are not an acceptable form of birth control in this study because most oral contraceptives are hormonal similar to progesterones and this can interfere with the study.

If you become pregnant at any time during the trial, you will be withdrawn from the trial and Safety Follow-up procedures should be completed. You will be followed by your doctor until completion of the pregnancy.

NEW FINDINGS

We will inform you if we become aware of any relevant new findings related to the research drug Sodium Cridanimod that may affect your willingness to continue in this study. If this happens, the study doctor will discuss with you whether you want to continue in the study. If you decide to continue, you will be asked to sign an updated consent form that would include the new information. If new information becomes available and the study doctor thinks that it is in your best interests to withdraw from the study, the reasons will be explained to you.

BENEFITS

You may or may not have a health benefit from participating in this study. Others may benefit in the future from the knowledge gained from this study.

PAYMENT FOR PARTICIPATION

You will not be paid for your participation in this study.

ALTERNATIVE TREATMENTS

Alternatives to taking part in this study:

- you may choose to take part in a different study, if one is available, or
- you may choose no treatment but you may want to receive comfort care to relieve symptoms, or
- you may continue your current treatment.

CONFIDENTIALITY

Authorization to Use and Disclose Protected Health Information (PHI)

Health information that could identify you, such as your social security number, medical record numbers, date of birth, etc. is called Protected Health Information, or “PHI.” During your participation in this research study, the study doctor and his/her study staff will collect or record PHI about you. This section provides information about how your medical records and health information (your “records”) will be used and shared in this research study. Your records may include information about your blood samples, biopsies, laboratory results, MRI or CT scans, physical examinations, adverse events, medical history and

any other data collected or reviewed during the course of the study as described in this consent form. Your records may also include information about treatment and tests you had before the study. Your study records will be assigned a code number by the study team; this code number will be used to identify you as a research subject without identifying you personally.

Your PHI is protected by laws in the U.S. and Europe. These laws require that research subjects receive written notification about the use and sharing of their PHI. In addition, it requires researchers (like the study doctor) to ask research subjects for permission to use and disclose their PHI for the purpose of a research study.

Your signature on this Informed Consent form authorizes your study doctor and study staff to use your records to carry out this study. You have the right to refuse to authorize this and not sign this consent form. However, you may not participate in this study unless you give this authorization to use and disclose your PHI.

By signing this form, you also allow the study doctor to disclose your records to the Sponsor. Your study information will be recorded on study forms and sent to the study Sponsor, Xenetic Biosciences and their representatives in this study. Your study records may be reviewed by the Sponsor, by representatives of the Sponsor, by this facility and the facility's Institutional Review Board / Independent Ethics Committee (IRB / IEC), or central IRB / IEC, by governmental regulatory agencies (such as the Food and Drug Administration [FDA], or any European Medicines Agencies). Study records will be kept confidential to the extent provided by law. Your name or other identifying data will not be used in any report or publication of this study.

All of your records, including this signed consent form, might also be reviewed or copied by the U.S. Food and Drug Administration (FDA) or by other regulatory agencies in other countries. These agencies might review your records to check the information collected in this study, to check how the study was conducted or for other uses allowed by law.

In addition, in the event that the Sponsor grants rights to the product being investigated in this study to another company to allow that company to promote, sell, or distribute the product, your study records may be disclosed and used by that company. As described above, your study records will be assigned a code number by the study team and you will not be identified by name in study records disclosed to other companies.

The laws regarding PHI require your study doctor to protect the privacy of your records. However, absolute confidentiality cannot be guaranteed because of the need to disclose information as described above. In addition, after your study doctor discloses your records to others, then the law may no longer protect your PHI.

You have a right to see and copy your research study records. During the study you will not have access to your records. You will have the right again to see and copy your records after the research is complete.

If you decide to stop participating in this research study, including the sub-studies, you may also end your authorization to use and share PHI. To cancel your authorization, you must notify your study doctor in writing. If you cancel your authorization, no new health information that can identify you will be gathered from you. However, information already collected cannot be removed from the study records, and may still be used and given to others if necessary for the research to be reliable. If you cancel your authorization, you will not be allowed to continue your participation in this study.

This authorization will expire 50 years from the date you sign it unless you revoke (cancel or withdraw) it sooner.

COMPENSATION FOR INJURY

If you have suffered an illness or injury that is determined to be directly caused by the administration of the study drug or the properly-performed study procedures (including sub-studies), the study sponsor will pay all reasonable and necessary medical expenses to treat that illness or injury. These medical expenses will be covered by the sponsor`s contracted insurance company. Reimbursement by the study sponsor for the treatment for any illness or injury that is not a direct result of study drug or study-related procedures will not be provided. Compensation (payment) for non-direct damages, such as lost wages, disability, or discomfort will not be provided. You will not waive any of your legal rights by signing this consent form. For instance, your legal right to claim compensation for injury where you can prove negligence is not affected by signing this consent form.

Further information regarding medical treatment for research-related injuries can be obtained from the study doctor or study staff. You must notify the study doctor immediately of any research-related injury.

Your obligation as a study participant is to:

1. Provide a complete medical history and answer all questions truthfully.
2. If you plan to undergo any other medical treatment during this study, or begin taking any new medications, you must tell the study doctor or study staff in advance.
3. If you suffer any injury or unexpected reaction to the medication you receive as a part of this study, you must notify the study doctor immediately.
4. If you suffer any injury or unexpected reaction to the medication you receive as a part of this study, you must seek treatment in accordance with the direction of the study doctor.

COSTS

The study medication (Sodium Cridanimod and megestrol acetate) will be provided at no cost while you are in this study. The cost of any other medications that you may use during the study will be your responsibility. The Sponsor of the study will cover the costs for any study related tests, exams and procedures, including sub-study procedures.

WHO TO CONTACT WITH QUESTIONS

You have the right to ask any questions concerning this study at any time.

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the study doctor at the telephone number listed on page one of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in a research study being conducted by the study doctor listed on page one of this document.

If you have any questions about your rights as a research subject, and/or concerns or complaints regarding this research study, you should write to (enter IRB Name, address, phone). An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects.

Please indicate below whether you want us to notify your primary care physician or your specialist of your participation in this study.

_____ Yes, I want the study doctor to inform my primary care physician/specialist of my participation in this study.

_____ No, I do not want the study doctor to inform my primary care physician/specialist of my participation in this study.

_____ I do not have a primary care physician/specialist.

_____ The study doctor is my primary care physician/specialist.

Consent to Participate in the Study

A Phase 2, Single Arm, Two Period Study of Sodium Cridanimod in Conjunction with Progestin Therapy in Patients with Endometrial Carcinoma

I have read the information in the consent form and have discussed the study including compensation in the case of study-related injury and Institutional Review Board approval with the study doctor or study staff. All questions about the study have been answered to my satisfaction. I may withdraw from the study at any time or refuse procedures without affecting my ongoing clinical care. I consent to participate as a research subject in this study by signing this form. I will receive a copy of the signed Consent form.

By signing this informed consent form, I have not waived any of the legal rights that I otherwise would have as a subject in a research study.

Signature of Subject	Date	Time

Printed Name of Subject

Signature of Person Obtaining Consent (Investigator or Designee)

I have explained the above study, and discussed with this research subject, as well as answered their questions. I certify that, to the best of my knowledge, the research subject signing this consent form understands the nature, demands, potential risks and benefits involved in participating in this study.

The subject will be given a copy of their fully signed Informed Consent form.

Signature of Investigator / Designee	Date	Time

Printed Name of Investigator / Designee

CONSENT TO PARTICIPATE IN OPTIONAL PK SUB-STUDY (DURING TREATMENT PERIODS 1 and 2)

An important objective of this study is to investigate the possible pharmacokinetics (PK) of megestrol acetate when administered alone (Treatment Period 1), and the drug-drug interactions of Sodium Cridanimod and megestrol acetate when administered together (Treatment Period 2).

You will not get health benefits from this sub-study. The researchers leading this optional sub-study hope the results will help other people with cancer in the future.

The PK Sub-Study involves taking additional blood samples from you as follows:

- At 10 timepoints during Treatment Period 1: At Study Visit -3, before administration of megestrol acetate, and 1, 2, 3, 4 and 6 hours after administration. Blood samples will additionally be taken 1 day (24 hrs) later, 2 days (48 hrs) later, 3 days (72 hrs) later, and 4 days (96 hrs) later.
- *Subjects who are PrR negative will not participate in the Treatment 1 portion of the PK Sub-Study.*
- At 15 timepoints during Treatment Period 2: At Study Visit 1, before administration of the study drugs and at 15, 30, 45, 60 and 90 minutes, 2, 3, 4 and 6 hours after administration. Blood samples will additionally be taken on Days 3, 7, 10 and Visits 3 and 4 of Treatment Period 2 prior to the administration of both Sodium Cridanimod and megestrol acetate.

Your samples will be sent to a special laboratory for use in the study described above. The samples will be kept until they are used.

I agree to participate in the optional PK Sub-Study, and have my specimens collected. I agree that my specimen samples and related information may be used for the PK Sub-Study described above.

_____	_____	_____
Signature of Subject	Date	Time

_____
Printed Name of Subject

Signature of Person Obtaining Consent (Investigator or Designee)

I have explained the above study, and discussed with this research subject, as well as answered their questions. I certify that, to the best of my knowledge, the research subject signing this consent form understands the nature, demands, potential risks and benefits involved in participating in this study.

The subject will be given a copy of their fully signed Informed Consent form.

_____	_____	_____
Signature of Investigator / Designee	Date	Time

_____
Printed Name of Investigator / Designee

I agree that my study doctor, or their representative, may contact me or my physician to see if I wish to learn about results from this optional PK Sub-Study.

YES NO Initials: _____