INSTITUTE: National Institute of Child Health and Human Development

STUDY NUMBER: 02-CH-0287 PRINCIPAL INVESTIGATOR: Lynnette Nieman, M.D.

STUDY TITLE: Treatment of Leiomyomata with the Selective Progesterone Receptor Modulator CDB-2914

Latest IRB Review: Continuing Review 06/25/03
Latest Amendment Approved: Amend C 10/14/03
Women with Fibrosis

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Nature of the Study

This study evaluates the drug CDB-2914, a new possible treatment for uterine fibroids in pre-menopausal women. CDB-2914 is a man-made hormone with a chemical structure similar to the hormones cortisol and progesterone. It blocks the action of progesterone, a hormone made by the ovaries that is necessary for maintaining pregnancy. In studies done at the NIH, a single 100 or 200 mg dose of CDB-2914 affected the menstrual cycle. When given within 14 days after the beginning of menstruation, CDB-2914 increased the time to produce a mature egg in the ovary, which resulted in a long cycle. When given within two weeks before the next period at a 100 or 200 mg dose, CDB-2914 caused an early menstrual period. When given at a single dose of 10 or 50 mg there was no effect on the menstrual cycle. CDB-2914 is chemically similar to the drug Mifeprex®, which has been FDA-approved for the termination of pregnancy. CDB-2914 is also an abortifacient in animals, but there are no plans to test for this in women. In women, Mifeprex® shrinks fibroid tumors and improves the pain of endometriosis. Since CDB-2914 and Mifeprex® have similar structures and effects on the menstrual cycle, we suspect that CDB-2914 might also be useful to treat these disorders.

To evaluate whether CDB-2914 causes fibroids to shrink, we will compare fibroid size, hormone levels and symptoms before and during daily administration of CDB-2914 (10 or 25 mg) or an inactive compound (placebo) for 10 – 14 weeks. Study participants will be women with fibroids who need and want hysterectomy for treatment of fibroids. They will undergo MRI and a saline hysterosonogram (ultrasound with fluid) of the uterus before and at the end of the treatment to count and measure fibroids; they will have blood drawn every 7 – 14 days, and will fill out a symptom calendar at home. Hysterectomy will be performed at the end of the treatment to evaluate the effects of the medication on the uterine and fibroid tissues, and to provide treatment for the study participant.

This study will be the first to evaluate the endocrine effects of long-term daily administration of CDB-2914 in pre-menopausal women. CDB-2914 has been given daily for 42 days to post-menopausal women without adverse side effects. While the daily dose of CDB-2914 in this study did not affect the menstrual cycle when given as a single dose, it is possible that daily doses will have an effect on development of the follicle (egg). To evaluate this possibility, we will measure blood hormone levels.

Another goal of this study is to assess whether daily use of CDB-2914 has any effects on the body's adrenal gland function. CDB-2914 is chemically similar to cortisol, the so-called stress hormone, which the adrenal glands produce to regulate salt and water balance. When given to post-menopausal women for 42 days, CDB-2914 did not affect adrenal function. It is possible, however, that longer treatment might have an effect.

Procedures of the Study

This study takes place during five menstrual cycles. The first, pre-treatment, cycle is done to find out about the unique timing of your menstrual cycle and to be sure that your ovaries work normally. During the next three menstrual cycles (or up to 102 days), you will be taking the study medication, CDB-2914 or a non-active treatment (placebo). You will be required to make several visits to the 9 East Day Hospital on the 9th floor of the NIH Clinical Center, each of which will require about an hour of your time. At the end of the treatment period, you will undergo hysterectomy at the Clinical Center, and will return afterwards for a routine post-operative check-up.

First Visit

This study involves an initial visit to be sure that you are eligible to participate. This visit will last about two hours and will include the following:

(1) You will answer questions about your health history (about 15 minutes) and have a complete physical examination (about 20 minutes) including a breast and pelvic examination,

(2) You will have a blood sample (about 4 teaspoons) drawn from a vein in your arm for testing of your blood count, liver and kidney function tests, and measurement of hormone levels, and you will provide a urine sample to test your urine,

(3) You will be taught to use a kit to test your urine at home for the presence of LH, a hormone that your body produces in large amounts just prior to ovulation (release of an egg from your ovaries). You will be given a menstrual calendar to record this "LH surge", as well as any days of vaginal spotting or bleeding, or any symptoms during the study, and

(4) You will fill out the SF-36 questionnaire asking about your quality of life.

You may be excluded from continuing in the study if there are significant abnormalities on exam or laboratory testing. If you have abnormalities on your screening tests you will be informed of these results and advised to have them evaluated further by your personal physician.

First (Pre-treatment) Cycle

In the first menstrual cycle of the study you will not be taking any medication. While at home you will begin daily urine testing for the LH surge on the 11th day of your menstrual cycle. Seven days after you detect the LH surge in the urine test you will return to the Clinical Center for a blood test of your hormone levels (2 teaspoons). If both the test results and the timing of your LH surge are appropriate, you will continue in the study. If not, you will receive partial remuneration for your participation up to that point.

You will also come to the Radiology Department on the first floor of the Clinical Center to have an MRI and a special ultrasound of the uterus to document the location, size and number of fibroids. MRI is used to view the body using radio waves and a magnetic field. You will lie in an imaging tube for approximately one hour. A contrast agent, gadolinium, is given by vein; it is approved by the FDA for this use. The special ultrasound is called a "saline hysterosonogram" and involves placing a speculum in the vagina, as if for a pap smear test, and then putting a very small amount of liquid inside the uterus, using a small plastic tube. An ultrasound examination then will be done by inserting a probe into the vagina. This probe emits and receives sound waves that can be used to form a picture of the internal structures. The sound waves are painless and do not pose a medical hazard to you. This procedure is done with an empty bladder and takes about 20 minutes. Occasionally the insertion of the vaginal probe or the fluid may be uncomfortable, but it is usually well tolerated.

Second through Fourth Menstrual Cycles (treatment phase)

On the first or second day of your menstrual cycle you must come to the Clinical Center to have a very accurate and reliable urine pregnancy test done. If you are not pregnant, you will start taking the study medication once a day on an empty stomach for three menstrual cycles or up to 102 days if your menstrual cycles are irregular or stop. If you do not have a tubal ligation, we advise that you use a barrier contraceptive, such as a diaphragm or condoms, while you are taking the study drug.

You will return to the Clinical Center 9 East day hospital at intervals during treatment to undergo safety blood monitoring, and/or endocrine blood evaluation.

1. You will return to the Clinical Center every two weeks to have blood tests (about 2.5 tablespoons or 36 ml) that will measure effects of the study medication on your hormones, blood count, blood chemistries and liver function.
2. At three times during the study you will collect urine for 24 hours and bring it to the Clinical Center on one of your ultrasound visits. This will occur in your first, second and third menstrual cycles, or approximately once a month for the first three months if you are not having any menstrual flow. We will measure cortisol to check adrenal gland function.
3. A repeat transvaginal ultrasound will be done in the Department of Radiology on the first floor of the Clinical Center after 4 – 6 weeks of treatment to be sure that the fibroids are not growing too rapidly. A repeat saline hysterosonogram and MRI will be done within two weeks of surgery. These tests will be done to count the number of fibroids and measure their size.

Surgery

Surgery will be provided only to women completing the study to that point. However, if your condition no longer warrants a hysterectomy, you may be denied this procedure and this will not affect your remuneration.

1. You will be admitted to the 8 West in-patient ward at the Clinical Center for hysterectomy, either after the LH surge in the third treatment cycle, or in the follicular phase of the fourth cycle, or between 90 and 102 days of treatment. At that time you will hand in the menstrual cycle charts and symptom records and will complete the SF-36 quality of life questionnaire again. Blood will be drawn for measurement of CDB-2914 (8 mL, 1.5 teaspoons) and the study drug will be stopped. The study drug will not be provided beyond your participation in the study.
2. Hysterectomy will be done through an incision in the lower abdomen. This is a standard approach for the larger uterine size that we expect in this study because of the fibroids. Your ovaries will be removed only if it is medically indicated, which will be discussed with the surgeons. You will remain on 8 West for two to four days after surgery and will be discharged when medically indicated.

Post-Surgery Visit(s)

You will return to the 9 East Day Hospital for a routine post-operative check-up about 4-6 weeks after surgery. Once there are no problems related to the surgery, you will return to your non-NIH gynecologist for long-term care. If you have not had your ovaries removed, and your menses stopped during the treatment, you will monitor urine LH and to return 5 – 7 days after the kit is positive, for a blood withdrawal to measure progesterone (5 mL or 1 teaspoon).

Remuneration

We will remunerate you for your participation. This would amount to $100. This amount will be prorated to a lesser amount if you are unable or unwilling to complete the study. If hysterectomy is no longer indicated, you will receive the full remuneration for your participation to that time.

Benefits

You may benefit by receiving a physical examination, laboratory testing and hysterectomy for fibroids. If you receive CDB-2914, your symptoms may decrease and you may have an easier surgery if the fibroids become smaller, but it is not known if this will occur.

Risks and Discomforts

1. *Blood sampling* may result in temporary discomfort as the needle is inserted. There is a very small risk of bruising or infection at the needle stick site. The phlebotomist will use clean procedures to decrease this risk.

2. *Blood loss* from the blood sampling will not exceed the NIH guidelines for the amount of blood that can be safely drawn over a 6 week period (15 ounces, 450 ml).

3. *Transvaginal ultrasound* is a routine gynecologic procedure that uses an ultrasound probe placed in the vagina. The probe emits soundless, painless and medically harmless sound waves that provide a picture of your ovaries and uterus. Usually this is not uncomfortable and takes no more than 10 minutes. However, if insertion of the probe is painful, we will discontinue the procedure. There is no known risk associated with ultrasound testing. There is a very small risk of infection when the small plastic catheter and fluid are put in the uterus for the saline hysterosonogram. The risk of infection will be minimized using clean technique. There may be some cramping, lasting a few minutes, as the catheter and fluid are inserted.

4. *CDB-2914* does not have any known serious adverse side effects. No adverse effects were found with single doses of CDB-2914 (10 – 200 mg) given to about 120 healthy women or daily doses of up to 50 mg given to post-menopausal women for 42 days. However, it is possible that an unforeseen reaction or side effect could occur in this study, which uses 10 to 25 mg CDB-2914 for up to 102 days. For this reason you are asked to report any concerns or symptoms to the study investigators immediately. We will check your blood routinely for any evidence of bad effects on your liver, kidneys, and blood cell count. If any serious effects are detected on this blood testing we will contact you and stop CDB-2914. CDB-2914 has not had any bad effects on any of these organs when given to monkeys for up to 6 months. When given to rats at similar high doses for 6 months, some rats had liver enlargement. These rats received a very large daily dose of CDB-2914 that was approximately 100 times greater than the daily dose you may receive. For this study, you will be receiving a much lower dose of CDB-2914 in relation to your body weight, equivalent to only 1% of the dose the rats received. Because of the difference in the dose, the lack of bad liver effects in monkeys, and the lack of any bad effects in women, we do not expect any bad liver effects to occur in this study.

Because CDB-2914 is chemically similar to cortisol, a hormone produced by your adrenal glands, we are particularly concerned about symptoms that may reflect a blockade of cortisol effects. Such symptoms would include nausea, weakness, joint aches or pains, diarrhea or unusual fatigue. You must report these symptoms to the study investigators if they occur and persist for more than a day. We may ask you to return to the Clinical Center to evaluate whether such symptoms are caused by CDB-2914, or a common sickness with similar symptoms, like the "flu." Although women in previous studies at the NIH have not had these symptoms, it is possible that they may occur when CDB-2914 is given for longer periods of time.

5. The *24-hour urine* collections will involve some inconvenience but no risk. It requires you to collect all urine voided in this time period, place all collections in a single container and then carry this container (which may contain 1 – 2 quarts) with you to the Clinical Center. You will be provided appropriate receptacles and a discrete carrying bag to minimize the inconvenience.

6. There may be a small inconvenience involved in filling out the menstrual calendar and in filling out the SF-36 questionnaire. The confidentiality of your responses will be maintained to the extent allowable by law. Your responses to the questionnaire will be filed securely and your name will not be associated with your responses in either the analysis or the reporting of study results. Only the researchers involved in the study will see your answers.

7. You may experience unexpected vaginal bleeding or spotting at any point during the study. This may cause some discomfort or inconvenience that may be minimized by wearing, or carrying with you, a panty liner for the duration of the study.

8. *Hysterectomy* is a surgical procedure requiring hospitalization for up to 4 days afterwards. Although you will undergo hysterectomy because it is medically indicated for treatment of your fibroids, this a part of this research study, and has risks not related to the research. Complications of hysterectomy include infection at the surgery site (1%), damage to the bladder or bowel (1-2%), blood loss requiring transfusion (1-2%), and complications of anesthesia, including death (1:40,000). Blood clots in the pelvis, leg or lung are rare (1%), but do occur and may cause pain, and less commonly death (less than 1:1000). The pain of the surgery will be treated with appropriate pain medication. Because hysterectomy is a major abdominal surgery, you will not be able to drive a car or lift heavy objects for three weeks. You will not be able to work for at least 3 weeks.

9. *MRI* requires that you do not move, and you must lie in a closed space.

Patients are at risk for injury from the MRI magnet if they have pacemakers or other implanted electrical devices, brain stimulators, dental implants, aneurysm clips (metal clips on the wall of a large artery), metallic prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, implanted delivery pump, or shrapnel fragments. Welders and metal workers are also at risk for injury because of possible small metal fragments in the eye of which they may be unaware. You will be screened for these conditions prior to the study, and if you have any of these conditions, you will not receive an MRI scan. If you have a question about any metal objects being present in your body, you should inform the physician. In addition, all magnetic objects (for example, watches, coins, jewelry, credit cards) must be removed before entering the MRI scan room. Women who are pregnant are excluded from MRI. Therefore, all women of childbearing potential will have a pregnancy test performed, which must be negative, before proceeding.

During part of the MRI you will receive a contrast agent into your vein that is gadolinium-based. A contrast agent changes the relative brightness or contrast on the MRI image under some conditions. The gadolinium -based contrast agents are approved by the FDA for use with MRI imaging. The vast majority of patients receiving gadolinium-based contrast agents have no symptoms related to the injection of this medication. Mild symptoms that may occur include coldness in the arm at the time of injection, a metallic taste, headache, and nausea. In an extremely small number of patients, more severe symptoms have been reported including shortness of breath, wheezing, hives, and lowering of blood pressure. You should not receive gadolinium-based contrast agents if you previously had an allergic reaction to them. You will be asked about previous allergic reactions to gadolinium-based contrast agents before it is administered.

10. *Disruption of the menstrual cycle* is a possible risk. While, there was no effect on cycle length after a single dose of CDB-2914 at a 10 mg dose in previous studies, it is possible that chronic administration at up to 25 mg daily will affect development of an egg. This might result in lack of menses, or irregular menses. While a disruption of menses for three months or irregular menses does not have significant medical consequences, it may be distressing or inconvenient for you.

11. *Time* involved in multiple visits and in performing in home testing may be a discomfort. Every effort will be made to streamline the visits. After the first screening appointment, visits are estimated to require no more than one hour. The MRI and saline hysterosonogram visits may take a few hours, depending on how they can be scheduled. Failure to comply with the study procedures may result in your termination from the study.

12. *Anemia* is a risk of the study. While the total blood withdrawal falls within NIH guidelines, iron deficiency anemia is a potential risk. This risk will be minimized by including only women with hemoglobin > 10 g/dL.

Confidentiality and use of blood and tissue samples:

We will record your name with the tissue samples obtained from you, including blood, urine, and uterus specimens. Initially these samples will be used as described above for studies at the NIH. The measurements of CDB-2914 in your blood will be done at a commercial laboratory, and also by our collaborators in Paris, France. The samples will be coded for those measurements, and the code will be kept with the investigators at the NIH with your name.

Additionally, the samples may be stored for a long period of time, with your name, and used for different studies related to CDB-2914 than those we originally plan. For example, if we discover new effects of CDB-2914 on a protein in the blood, we may evaluate that effect in your stored samples.

It is possible that future studies may involve sharing your tissue with other investigators. If this is done, information about your medical condition may also be shared for the purpose of the future study. However,

information about you would be sent with a coded identification so that your name would not be linked to the information received by the other investigators. These studies would only involve investigations of fibroids or uterine tissue or effects possibly related to CDB-2914.

Your medical records are kept confidential to the extent allowable by law. Results of tests performed with the tissue obtained from you will be kept confidential. However, access to your records will be allowed to individuals carrying out this study, so that appropriate information can be collected and possibly published in scientific journals. Your results may also be provided to the Food and Drug Administration (FDA) and similar agencies outside the United States to determine whether CDB-2914 is safe and effective for treating fibroids. For this purpose, your results would be provided without identifying your name. Occasionally the FDA audits medical records directly at the Clinical Center as part of their regulatory authority.

The results of research tests performed with the blood and tissue obtained will not routinely be provided to you. By agreeing to participate in this study you do not waive any rights that you may have regarding access to and disclosure of your records. For further information on these rights, please contact the principle investigator.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or other authorized people.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Dr Lynnette Nieman; Building 10, Room 9D42, Telephone: 301 496-8935. Another researcher you may call is Dr. Clariss Nahari; 301-496-5800.

You may also call the Clinical Center Patient Representative at 301-496-2626.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/Legal Representative _____ Date _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/Guardian _____ Date _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM JULY 24, 2003 THROUGH JULY 24, 2004.

Signature of Investigator _____ Date _____ Signature of Witness _____ Date _____