UNIVERSITY OF WASHINGTON
CONSENT FORM

A Pilot Trial of 13-*cis* retinoic acid (isotretinoin) for the Treatment of Men with Azoospermia

Researchers:
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This is the 24-hour emergency telephone number for the paging operator: 206-598-6190. Ask the operator to page one of these study doctors: Drs. Amory, Thomas Walsh or Kevin Ostrowski.

Researchers' statement

We are asking you to be in a research study. The purpose of this consent form is to give you the information you will need to help you decide whether to be in the study or not. Please read the form carefully. You may ask questions about the purpose of the research, what we would ask you to do, the possible risks and benefits, your rights as a volunteer, and anything else about the research or this form that is not clear. When we have answered all your questions, you can decide if you want to be in the study or not. This process is called "informed consent." We will give you a copy of this form for your records.

PURPOSE OF THE STUDY

Our previous work has suggested that men with infertility may have low levels of the active form of Vitamin A, called retinoic acid, in their testes. We did an initial study giving men with low sperm counts retinoic acid to increase their sperm counts and it worked in some of the men. We are enrolling twenty men with infertility due to no apparent sperm (azoospermia) in a pilot research study here at the UW. Our goal is to see if retinoic acid administration over thirty-two weeks can allow for some sperm production and help infertile men become fathers through in vitro fertilization, which requires at least some sperm. All men will receive retinoic acid treatment (there is no placebo group or blinding in this study).

STUDY PROCEDURES

This is a study to determine the impact of retinoic acid administration on the presence of sperm in the ejaculate in men with no sperm present in ejaculated fluid (azoospermia).

To participate in the study you must be between 21-60 years of age and have infertility from absent sperm in the ejaculation, but be otherwise healthy. If you are currently taking anabolic steroids, illicit drugs or drink more than 4 alcoholic beverages daily, you cannot participate in

this study. If you take medications such as lupron, ketoconazole, finasteride, dutasteride, methadone, tetracycline, phenytoin, or lithium you cannot participate in this study.
Subjects' medical records may be used to verify their medical history, hospitalizations, and concomitant medications use throughout the study.

The study involves 13 visits spaced out over 12-18 months.

All Study Visits will take place at the University of Washington

Screening can last between 8-60 days – consists of two visits, separated by one week.

Screening Visit 1 [Approximately 1 hour]

Prior to any study procedures, you will be asked to read this informed consent form and ask any questions you may have. If you want to participate, you will then sign this consent form along with Dr. Amory. Next, Dr. Amory will review your medical history, ask you about the medications that you are taking and perform a physical examination, including measurement of your testicle size. A blood sample (about 2 tablespoons) will be drawn to assess your general health and measure the levels of hormones and vitamin A and retinoic acid levels in your blood, and you will be asked to complete a 9-question PHQ-9 questionnaire about your mood to screen for and measure depression. You may refuse to answer any question during this visit during the medical history or on the questionnaire. Finally, we will ask you to provide a sperm sample by masturbation after a minimum of 48 hours of no sexual activity to determine your sperm count, concentration, motility (movement) and morphology (appearance).

Screening Visit 2 (approximately 20 minutes)

You will have a brief check of your blood pressure and pulse and be asked if you are taking any new medications. You will be asked to provide a 2nd baseline sperm sample after a minimum of 48 hours of no sexual activity. If you are eligible and participate in this study, you may not donate blood during treatment and for 12 weeks after treatment is completed.

Treatment Visits. There are nine visits in the treatment period: week 0, 4, 8, 12, 16, 20, 24, 28 and 32. All visits are + 6 days. We will collect blood samples after 8 hours of fasting. You may feel some discomfort from fasting.

Treatment Visit 1-8 (approximately 45 minutes each) + 6 days

Treatment Visit 1 is day 1 of treatment.

You will have a brief check of your blood pressure, pulse, and weight, and one of the study doctors will review how you are feeling and ask you about concomitant medications and adverse events. If you are taking a medication that is listed as disallowed you may be disallowed from the study. The doctor will perform a brief physical examination, including measurement of your testicle size. A blood sample (about 2 tablespoons) will be drawn (weeks 8, 16 and 24) to assess your general health and measure the levels of hormones and vitamin A and retinoic acid levels in your blood, and you will be asked to complete a 9-question PHQ-9 questionnaire about your mood. You may refuse to answer any question during this visit during the medical history or on

the questionnaire. We will also ask you to provide a sperm sample by masturbation after a minimum of 48 hours of no sexual activity. Lastly, you will be given a four-week supply of 13-*cis* retinoic acid (Isotretinoin) and a medication log and be instructed how to take and record your study drug use. You will take one capsule of 20 mg of Isotretinoin twice a day, with meals, for a period of 32 weeks. We will ask that you not take study drug on the mornings of clinic visits, and bring all unused study drug to each visit. You will need to fast (no food or drink other than 4 to 6 ounces of water or non-sweetened clear liquids) for a minimum of 8 hours. If you have not fasted or abstained from sexual activity for semen sample collection, we will re-schedule your appointment.

Treatment Visit 9, (approximately 45 minutes), week 32 ± 6 days.

We will ask that you arrive fasting (no food or drink) for a minimum of 8 hours. You will have a brief check of your blood pressure and pulse and one of the study doctors will review how you are feeling and the presence of any new symptoms or possible side effects from the study medication and perform a brief physical examination, including measurement of your testicle size. A blood sample (about 2 tablespoons) will be drawn to assess your general health and measure the levels of hormones and vitamin A and retinoic acid levels in your blood, and you will be asked to complete a 9-question questionnaire about your mood. You may refuse to answer any question during this visit during the medical history or on the questionnaire. We will also ask you to provide a sperm sample by masturbation after a minimum of 48 hours of no sexual activity. We will ask that you **not** take study drug in the morning of your visit, and bring all unused study drug

Follow-up Visits 1 and 2 (45 minutes each), weeks 44 and 56 ± 14 days

We will ask that you arrive fasting (no food or drink) for a minimum of 8 hours. You will have a brief check of your blood pressure and pulse. One of the study doctors will review how you are feeling and the presence of any new symptoms and medications, and perform a brief physical examination, including measurement of your testicle size. A blood sample (about 2 tablespoons) will be drawn to assess your general health and measure the levels of hormones and vitamin A and retinoic acid levels in your blood (week 44 only). You will be asked to complete a 9-question questionnaire about your mood. You may refuse to answer any question during this visit during the medical history or on the questionnaire. We will also ask you to provide a sperm sample by masturbation after a minimum of 48 hours of no sexual activity

RISKS, STRESS, OR DISCOMFORT

Medical History: The interview with the study doctor and medical form includes questions about your medical history, which may cause you some discomfort or embarrassment. You are free to refuse to answer any of these questions.

Blood draws: Blood draws can cause some discomfort and occasionally lightheadedness, or fainting in some subjects. There is also a risk of infection or bruising around the site of the blood draw. A bruise may form where the needle enters the vein.

Laboratory results: We will share all of your sperm test results with you if you would like, including any sign of sperm in your ejaculate. If any of your blood tests are abnormal, we may have you return for a repeat blood draw. If any of the results are abnormal, especially if it is

worrisome in terms of your health or means you cannot participate in the study, we will let you know immediately.

Confidentiality: our identity will be kept confidential. However, in the very unlikely event of a breach of confidentiality, there is a risk you would experience a feeling of invasion of your privacy.

Medications: 13-*cis* retinoic acid therapy (Isotretinoin) is commonly used for the treatment of severe acne. It can be associated with significant side effects including tiredness (10%), eczema of the skin or inflammation of the lips (15%) and rarely depression (<1%). If these side effects become severe, it may be necessary to stop drug administration. If you experience study-related injury, illness, or distress, please contact Dr. Amory, Walsh or Ostrowski at the numbers above immediately.

If taken by a pregnant woman, isotretinoin can cause birth defects, so should never be administered to women at risk of pregnancy without the use of adequate contraception. Importantly, despite many years of use, there is no evidence to suggest birth defects in the children of women who conceived while their husbands were taking isotretinoin. As a result, men using isotretinoin are not required to use condoms for intercourse. In our previous study using isotretinoin in infertile men, only extremely small amounts of isotretinoin were present in the semen of men using isotretinoin. These concentrations were too low to expose a woman to any risk.

Because 13-*cis* retinoic acid (Isotretinoin) treatment for infertility is experimental, it is unknown if treatment will increase sperm production. Please know that we will provide you with any information developed during the study that might affect your willingness to participate.

ALTERNATIVES TO TAKING PART IN THIS STUDY

You are participating in this study as a man with infertility due to a reduced sperm count. The alternative to participation is to not participate, and to use donor sperm to treat your infertility.

BENEFITS OF THE STUDY

Information from this study may be useful in the treatment of men with infertility from absent sperm in the ejaculate.

MEDICAL RECORD INFORMATION

Policies require that we put information about this research into your permanent medical record at UW Medicine. If you do not have a medical record at UW Medicine, one will be created for you even if your only connection with UW Medicine is as a research subject.

Information that will be put into your medical record:

1. Your name, address, telephone number, date of birth, social security number, health insurance information, billing information, and any other information you provide on the hospital or clinic information form.

2. Information about this research study:

   - Name of the study, described as: [***RRRRA, FOUR***]
   - The name of the researcher
   - The name of the study coordinator
   - Contact phone number for the study
   - Contact email address for the study
   - Emergency phone number for the study
   - Expected start and end dates for your time in the study

Who will have access?

This medical record will be permanent. It will be stored with all other UW Medicine medical records. A copy of your record may also be stored on the secure UW Medicine medical record computer system. Access to medical records and the computer system is restricted to authorized staff only with passwords for the system. Only UW Medicine staff and people who have legal access to your medical record will be able to see it. This may include your insurance company and government regulatory agencies. If you have already given permission to anyone (such as your health insurance company) to look at your medical record, they may receive this research information if they ask for a copy of your medical record.

Your health insurance

Though very unlikely, this could have some effect on what your health insurance company (but not Medicaid or Medicare) is willing to pay for while you are in the research. If this infrequent situation happens, we may be able to help by giving you some information to share with your health insurance company.

SOURCE OF FUNDING

The study team and/or the University of Washington is receiving grant funding for this research from the Eunice Kennedy Shriver National Institute of Childhood Health and Human Development, the part of the National Institutes of Health that performs infertility research.

CONFIDENTIALITY OF RESEARCH INFORMATION

Your lab results and semen data will be kept in a private research chart in the lab, and will not be placed in your medical record.

All study data will be confidential with a link between your data and your assigned study number. This link will be retained until 1/1/2024 after which point your data will be made anonymous.

All of the information you provide will be confidential. However, if we learn that you intend to harm yourself or others, we must report that to the authorities.

Government or university staff sometimes review studies such as this one to make sure they are being done safely and legally. If a review of this study takes place, your records may be examined. The reviewers will protect your privacy. The study records will not be used to put you at legal risk of harm.

The U.S. Food and Drug Administration (FDA) reserves the right to review study data that may contain identifying information.

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.

OTHER INFORMATION

All study treatment procedures will be provided at no cost to you throughout your participation in this study. You will receive up to $470 for completion of this study to cover the costs of your time, travel, and inconvenience. You will receive $30 after the 1st screening and $20 after the 2nd screening visit. You will receive $40 for each study visit during the treatment phase and $30 for each of the two follow-up visits. If we request that you return to repeat a screening lab test, you will receive an additional $25 for your time and inconvenience. In addition we will provide you with parking validation or a metro transit token. If you are not a citizen of the United States and do not have a social security number, we are required to withhold 30% of your payment for taxes.

The researchers will keep the link between your name and study number for up to six years, which means they will destroy the link no later than January 1st, 2024. Serum samples from study visits may be stored for future testing. In particular, we are interested in trying to identify serum biomarkers of response to Isotretinoin therapy. We will keep your blood samples, labeled with your study identification number and initials for 5 years after the end of the study. After that point, we will remove all identifying information from your blood samples. We keep these samples in the event that more effective ways for understanding the relationship between retinoic acid and sperm production become available.

By signing this consent form, you agree to allow the researchers to decide what to do with any surplus samples (blood and semen) removed from your body during the research described above. No specimens will be shared. No sperm will be used to fertilize an egg for research purposes. You will be told if the researcher has any current personal interest, such as any economic interest, related to performing this research (there is none). The semen samples will be stored for future analysis as well for up to six years to understand the presence of Isotretinoin in the semen. The serum samples may be used for the assessment of newly developed hormone assays or bioassays when available. You may contact the investigator to discard your samples after the aims of the study have been met. Data collected during study participation cannot be withdrawn.

You must inform your study doctor of any drugs you use during the study and of any illness that develops (of any type or severity) while participating in this study.

Your taking part in this study may be stopped at any time. The study doctor can stop the study without your consent for the following reasons:

- it appears to be medically harmful to you;
- missing scheduled clinic visits;
- refusal to complete required tests;
- development of a medical condition(s) or serious side effect(s) that may pose a health risk to you;
- you do not meet the study requirements;
- the study is cancelled;
- for administrative reasons including enrollment (the target number of subjects have been enrolled) or
- for any other reason

Your participation is voluntary. You may refuse to participate and are free to withdraw from this study at any time without penalty or loss of benefits to which you are otherwise entitled. If you do withdraw, however, we will ask you to return to the clinic for any study tests necessary in insure your safety and well-being. Your decision will not adversely affect your medical care.

RESEARCH-RELATED INJURY

If you think you have a medical problem or illness related to this research, contact the study staff [Dr. Amory, (206) 616-1727] right away. You can tell the researcher in person or use the 24-hour emergency telephone number for the paging operator, (206) 598-6190. If you are injured as a result of being in this study, necessary medical treatment will be offered at a UW Medicine facility..

Printed name of study staff obtaining consent Signature Date

Subject's statement

This study has been explained to me. I volunteer to take part in this research. I have had a chance to ask questions. If I have questions later about the research, or if I have been harmed by participating in this study, I can contact one of the researchers listed on the first page of this consent form. If I have questions about my rights as a research subject, I can call the Human Subjects Division at (206) 543-0098 or call collect at (206) 221-5940. I give permission to the

researchers to use mymedical records as described in this consent form. I will receive a copy of this consent form.

Printed name of subject	Signature of subject	Date

Copies to: Researcher
Subject
Subject's Medical Record (if applicable)

Appendix 1: Schedule of Events

		Screening		Treatment		Follow-up	
	Visit #	S1	S2	T1	T2-T9	F1	F2/exit
	Study Day	-60 to -1	-53 to 1	1	Wks: 4, 8,12,16, 20, 24, 28, 32	Wk 44	Wk 56
Administrative	Informed consent/HIPAA	X					
	Vital Signs	X	X	X	X	X	X
Medical	Medical History	X					
	Physical Exam	X		X	X	X	X
	AE & Con Med	X	X	X	X	X	X
	Semen Analysis	X	X	X	X	X	X
	PHQ9 Questionnaire	X		X	X	X	X
Blood Sampling	CBC, Chemistry/Lipids, CK	X		X	X**	X	X
	FSH, LH, T & Retinoids	X		X	X**	X	X
Drug Administration	Dispense Study Meds			X	X*		
	Dispense study med log			X	X*		
	Collect and review med log				X		
	Collect unused study meds				X		
Reimbursement ($)		30	20	40	40	30	30

- Visit T9, week 32: No drug or study log dispense **Blood draws only week 8, 16, 24 and 32.

Abbreviations:

- HIPAA: Health insurance portability and accountability act
- PHQ9: Patient health questionnaire, #9
- FSH: follicle-stimulating hormone
- LH: luteinizing hormone
- T: testosterone
- AE: adverse event
- Con Med: concomitant medications
- S1/S2: screening visit 1/2
- T1-T9: treatment visits 1-9
- F1/F2: follow-up visit ½
- Wk: week