

Approved by the Nemours IRB.	Valid from: 05/22/2009 through 04/02/2010	IRB #:	09-019
Abbreviated Study Title:	Estrogen dosing in Turner Syndrome: Pharmacology and metabolism: Protocol #2		

NEMOURS Children's Clinic
PARENTAL PERMISSION FOR PARTICIPATION IN A RESEARCH STUDY

You have been asked to permit your child to be in a research study. This form explains the research, your child's rights as a research participant, and any responsibilities that you may have as a result of your child's participation. You should understand the research study before you agree to permit your child to be in it. ***Read this permission form carefully. You may also talk with your family or friends about it. A research team member will answer any questions you and your child have before you make a decision.***

1. WHAT IS THE TITLE OF THE STUDY?

Estrogen dosing in Turner Syndrome: Pharmacology and metabolism. Protocol # 2

2. WHO IS IN CHARGE OF THE STUDY AT NEMOURS?

Principal Investigator: Nelly Mauras, MD
Chief Division of Endocrinology and Metabolism
Nemours Children's Clinic – Jacksonville, FL

Co- investigators: Judith Ross, MD
Nemours Children's Clinic – Jefferson University
Jorge Daaboul, MD
Nemours Children's Clinic-Orlando, Florida
Mark Kummer, MD
Nemours Children's Clinic- Pensacola, Florida

Fellow: Martha Taboada, MD
Nemours Children's Clinic

Address: Nemours Children's Clinic -JAX
807 Children's Way, Jacksonville, FL 32207

Nemours Children's Clinic – ORL
1717 South Orange Ave, Orlando, FL 32806

Nemours Children's Clinic – Pensacola
5153 North 9th Ave, Pensacola, FL 32504

Nemours Children's Clinic/Thomas Jefferson University
Suite 726, 1025 Walnut St, Philadelphia, PA 19107

Telephone numbers: Florida: (904) 697-3600 (operator - Jacksonville) ext. 3674 or
(800) SOS –KIDS (Nemours-Long Distance Operator) ext. 3674
(904) 697-3674 (NCC- Division of Endocrinology- Jax)
Philadelphia: 215-955-1648

3. WHO SHOULD RESEARCH PARTICIPANTS CONTACT ABOUT THEIR RIGHTS?

If you have questions about your child's rights as a research subject, what to do if your child is injured, if or your child would like to offer input or obtain information, or if you cannot reach the investigator or want to talk to someone else who is not involved with this research, you may contact the persons listed below.

Tim Wysocki, Ph.D., Chairperson, Nemours-Florida Institutional Review Board at (904)-697-3415.
Paul Garfinkel, MSH., Director, Nemours Office for Human Subjects Protection, at (904) 697-4023.
(Nemours Long Distance Operator) (800) SOS-KIDS (800-767-5437)

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Website: <http://www.nemours.org/research/nohsp.html> . Email address: NOHSP@nemours.org.

4. WHAT IS THE PURPOSE OF THE STUDY?

We want to test 2 different preparations of estrogen (one given by mouth, one via a skin patch) in different doses, to test how the body responds to estrogen differently, depending on the way the estrogen is given. We hope to learn whether the form of estrogen affects your body composition (the amount of body fat vs. muscle) and other blood tests related to blood cholesterol and other hormones.

5. WHO IS PAYING FOR THE STUDY?

The Genentech Center for Clinical Research in Endocrinology, a private peer-reviewed foundation that funds pediatric endocrine work is paying Nemours to conduct this study.

6. WHO CAN BE IN THE STUDY?

Girls/ Young women with Turner Syndrome, diagnosed by blood test, between the ages of 13 -20 yrs will be asked to participate. Participants should have completed or nearly completed their growth; participants should not have received growth hormone therapy for at least 6 months prior to participating in the study. Participants should not have diabetes, obesity or inflammatory bowel disease such as ulcerative colitis or Crohn's disease. She cannot participate if she smokes. Participants cannot be smokers. If participants have thyroid disease they should be on adequate treatment.

There may be some reasons (some other illnesses) why your child cannot be in the study. If this happens, the study staff will discuss it with you.

7. HOW MANY OTHER PEOPLE WILL BE IN THE STUDY?

We are seeking to enroll 40 girls with Turner Syndrome that meet the criteria for participation listed above among the participating centers.

8. HOW LONG WILL PARTICIPATION IN THE STUDY LAST?

The study will last up to 14 months. There will be a visit at the beginning (baseline), 6month and 12 months which may take up to 3-4 hours each. The visits at 1 and 2 months are just for a laboratory blood draw and should be just 10 min plus the routine waiting time for the blood draw. The rest of the visits will be routine, every 3 months.

9. WHAT ARE THE RESEARCH PROCEDURES?

Your child will first have a full physical exam to see if she qualifies for the studies. If she is taking any estrogen medications, she will need to stop it at least 6 weeks before the studies begin.

Your child will come to a special unit at the hospital the morning of the studies. She will have a test called indirect calorimetry which is performed after an overnight fast. This requires breathing through a mouthpiece using a nose clip (similar to a snorkeling gear) for a few minutes. This will determine the amount of fat, sugar and protein burned and the overall energy needs. Also your child will be asked to urinate in a cup during these visits. This test will be also performed at 6 months and at 12 months visit.

In addition, two special studies will be done to measure your total body fat. One is by an instrument called a DEXA scan; this is similar to an X-ray, and it has a small amount of radiation. In this test your child will have to hold very still while lying down for a few minutes. We will also use a caliper, which is an instrument that measures your body fat by pinching the skin. This does not cause any pain. These tests will be done on the first visit and then repeated at 6 months and 12 months.

Also, a blood test will be performed to measure certain hormones. A numbing cream may be put on the skin before the blood is withdrawn.

All participants will be assigned to one of 2 treatment groups (this will be at random, similar to flipping of a coin). One group will get estrogen either as pills taken by mouth daily or by estrogen patches applied on the skin twice a week. Doses will vary depending on the blood levels of estrogen starting with the lower doses and adjusting these doses up as needed to keep the levels in the normal range. The doses of the pills will be either 0.5 mg, 1mg or 2mg of 17B estradiol, Estrace®. For the patches we will use Vivelle® patch in either 0.0375 mg, 0.05 or 0.075 mg.

The estrogen will be taken for 21 days (3 weeks). In order to have menstrual cycle a second hormone also produced by the ovaries called progesterone will be given to both groups as a tablet daily for 7 days each month. Your child will start taking progesterone (in addition to the estrogen) from day 14 through day 21/ of each cycle. Then both medications will be stopped on day 21, for a total 7 days off. A menstrual period most likely occurs after this time. After the 28 days, she will re-start the cycle of medications as explained above.

Your child would need to have blood tests for the measurement of different hormones after one and 2 months on the estrogen. We will adjust your doses to keep the estrogen levels within the normal range based on the results. We will see her for visits every 3 months for a total on 12 months. At those visits your child's weight and blood pressure will be checked and blood will be withdrawn for the measurement of hormones, blood fat (cholesterol and the like) and pertinent factors that are regulated by estrogen in the body. We will save a small amount of blood each time for storage so we can measure other blood tests in the future that may become available and would be important to measure in young women with Turner Syndrome taking estrogens. The blood sample will be kept frozen in our research laboratory at Nemours. We will repeat the DEXA and calorimetry tests at 6 and 12 months also. The total treatment period is 12 months.

STUDY SCHEME

	Baseline Visit (randomization)	1mo	2mo	3mo	6mo	9mo	12mo
Clinic Visit	X			X	X	X	X
Blood draws	X	X	X	X	X	X	X
DXA (BMD and body composition)	X				X		X
Calorimetry	X				X		X

10. WHAT ARE POSSIBLE RISKS OF BEING IN THIS STUDY?

Any research has some risks (things that could make your child sick, make your child feel uncomfortable, or hurt your child). The risks with the most chance of happening to someone in this study are listed below. Also, there is a chance of other risks that almost never happen, or unknown risks.

Blood tests can cause pain and potential infection; however experienced personnel will use antiseptic techniques for the blood drawing. To decrease the pain we may use a numbing cream (Emla or LMX®). There is a small risk of allergic reactions with the cream. If you are allergic to this cream you should let your doctors know. The risks of problems with blood draws are very small.

The DEXA scan has minimal radiation and is less than that received in a flight between the east and the west coast. If she is wearing metal in her bones she may not be able to have this test or have a partial test. You need to share this with your child's study doctors.

The amount of estrogen given for both the oral and skin route are comparable to the amount produced in the body during the early part of the menstrual cycle. Estrogen, when given both orally and via skin patch, can be associated with fluid retention, nausea, vomiting, headaches, changes in

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appetite, mood and even increased risk of blood clots. These risks are, however, not different than those observed when taking estrogen as replacement therapy without participating in this study. Since you are not producing much estrogen, it has been our experience that estrogen administration in girls with Turner Syndrome is well tolerated when given as replacement therapy. The estrogen patches can cause irritation around the skin where they are placed causing redness, itching and burning sensation. This is not common, however, we will use a cream containing a mild amount of hydrocortisone to eliminate the inflammation and itching if it occurs. The places will be rotated and the patches changed twice weekly.

It is not known whether estrogen replacement affects blood pressure in Turner syndrome so at each visit we will be measuring your child's blood pressure with a blood pressure cuff.

Progesterone can be associated with headaches, nausea, vomiting, mood disorders and fluid retention as well. You are likely to have monthly periods during the study.

11. WHAT ARE POSSIBLE BENEFITS OF BEING IN THIS STUDY?

Your child's participation in this study will allow us to understand better how to best replace estrogen in young women with Turner Syndrome and how the different forms of estrogen affect body composition. These studies will shed light into better ways to treat girls who are deficient in the production of estrogen. Your child may receive a direct benefit from the study as it will provide estrogen therapy which is needed in Turner Syndrome

12. WHAT HAPPENS IF A PROBLEM OR INJURY RESULTS FROM THE RESEARCH PROCEDURES?

If your child gets injured by being in the study, you should tell one of the investigators. The investigators names, addresses and phone numbers are on the first page of this form. If needed, she will be treated for the injury. However your child will not be paid for the injury and neither Nemours Children's Clinic, nor the sponsor will pay for treatment. If your child needs treatment for a problem related to the study you might be asked to come to the clinic or you may be told to come to the closest emergency room.

Neither Nemours, Wolfson Children's Hospital nor the study doctors have a program to pay for medical care provided to treat the injury. If your child has health insurance, it may, or may not pay for the cost of treatment resulting from a study-related injury. If your child's insurance does not pay, you understand that you will may be responsible for paying for the cost of treatment.

13. IS BEING IN THE STUDY VOLUNTARY?

Being in this study is totally voluntary. Anyone who takes part in the study can stop being in it at any time. There will be no change to your child's usual medical care if you or your child decide not to be in the study or decide to stop being in the study. No one will be angry with you or your child, or treat your child any differently than before your child was asked to be in the study.

In the event that your child withdraws from the study, the study doctor may ask permission to continue study follow-up. You may ask the researcher to destroy your child's information or samples. Your request must be in writing. The researcher will tell you if this is possible.

14. WHAT OPTIONS ARE AVAILABLE OTHER THAN BEING IN THIS STUDY?

Your child may choose not to participate in this study and to start estrogen as prescribed by your child's Endocrinologist. Your child does not need to participate in the study to be treated with estrogen. Your decision of whether or not to allow your child to participate in this study will not affect your child's care at the Nemours Children's Clinic. If your child decides to participate, your child may stop and withdraw from this study any time. We will tell you and your child anything we learn during the study that may help you decide whether or not to allow your child to continue participating.

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15. CAN THE RESEARCHERS REMOVE SOMEONE FROM THE STUDY?

Yes, if your child is not following the study procedures or there is any side effect that makes it difficult to follow the study procedures

16. WHAT ARE THE COSTS OF BEING IN THIS STUDY?

All the study expenses will be paid by our grant and will be at no cost to you. The study visits and laboratories related to the study participation would be provided for free. You are responsible for the costs of routine care.

17. WILL PEOPLE BE PAID FOR BEING IN THIS STUDY?

We will provide you with \$50.⁰⁰ stipend for each of the 7 visits for a total amount of \$350 by the end of the study. If your child stop the study before completing it we will give your child the stipend only for the visits completed. No other or future compensation is available.

18. WILL I BE TOLD OF ANY NEW INFORMATION THAT MIGHT AFFECT MY WILLINGNESS TO PERMIT MY CHILD TO STAY IN THE STUDY?

Any new information that may change your mind about allowing your child to be in this study will be given to you. A committee called the Institutional Review Board (IRB) will review this study at least once per year. If the IRB finds that there is new information that you should know about while your child is taking part in this study, it will ask the study doctor to tell you about it. You may be asked to sign a new version of this form after discussing the new information with a member of the research team.

19. WHAT INFORMATION ABOUT MY CHILD WILL BE USED OR DISCLOSED?

The Nemours investigators will protect study information by keeping study records in locked offices or files and in password-protected computer files. The health information that will be used or disclosed for this research study includes the information obtained during the screening and laboratories described in the procedures section. This health information will be connected to one or more items that can identify research participants to those who will use the study data. Your child's health information will be used and/or disclosed to conduct the research study, for follow up of possible adverse events and for monitoring and audit purposes. If you sign this informed consent form, you are giving permission for the use or disclosure of the individually identifiable health information for the research study described in this form. The health information that will be used by the Nemours researchers and staff include information in a medical record, results of physical examinations, medical history, lab tests, or certain health information indicating or relating to a particular condition. The code used in the tubes for the blood samples may contain the subject's initials.

No identifiable health information will be disclosed to organizations other than Nemours unless requested by the family of the participant. This authorization to disclose protected health information will end when the research study is complete and analysis and publication have ended.

The health information listed above may be used by and/or disclosed to:

- the investigators listed on the first page of this consent and their staff
- drug companies providing us any study drugs
- the funding agency (Genentech Center for Clinical Research in Endocrinology)
- the U.S. Food and Drug Administration
- the U.S. Department of Health and Human Services
- other legitimate agencies of State and local government as required by law
- the Nemours Institutional Review Board (IRB) (The IRB is a group of people that reviews research activities. The IRB is responsible for the safety and rights of research participants); and
- Nemours internal audit staff.

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The research results may be presented at meetings or in print. Participants' identities will not be disclosed in those presentations. Identifiable health information about your child will be used by Nemours researchers and may be given to people outside of Nemours for this research. This is done to conduct the research study, to monitor the safety of research participants and for auditing. Federal law requires us to tell you about, and get your approval for research use and disclosure of health information that includes "identifiers" that can connect the health information to. (Names, initials, date of birth, addresses, phone numbers, and social security numbers are examples of identifiers.) This Identifiable health information is called Protected Health Information (PHI)

Use of Health Information by Nemours Researchers

The health information that will be used within Nemours includes all data collected for this study, as described in Section 9 of this form. Your child's identity will be protected as much as possible. Nemours protects your health information by storing records in files or computers that can only be used by authorized Nemours staff.

Disclosure of Health Information to Others

Information from this research study may also be contained in the Nemours' medical record along with the information about your regular office visits. This will help other doctors to know about the research study your child is in and give them extra information from the research that might help them take better care of her. The same information might also be seen by anyone who can look at your child's medical records, such as your insurance company. The PHI that will be given (disclosed) to people or groups outside of Nemours for research purposes it is checked in the table below:

Type of Identifiable Health Information:	Disclosed
History and Physical	X
Results of Procedures	X
X-Ray Reports	X
Demographics (information about race, ethnicity, gender, age)	X
Laboratory results	X

Limits on Protection of Privacy and Confidentiality

Only health care organizations have to follow laws and rules about protecting the privacy of health information. If health information containing peoples' identities is given to other kinds of companies or organizations, they are not required by law to safeguard the privacy and confidentiality of that information. Nemours expects these companies and organization to protect the privacy and confidentiality of research participants, but it is not possible for Nemours researchers to assure that this happens.

Government agencies that may look at records for this research study, including the above health information, include:

- The U.S. Food and Drug Administration
- The U.S. Department of Health and Human Services
- Other agencies of State and local government as required by law
- Governmental agencies in other countries
- Genentech Center for Clinical Research in Endocrinology

The research results may be presented at scientific meetings or in print. Participants' identities will not be disclosed in those presentations.

20. SIGNATURES:

I am making a decision whether or not to permit my child to participate in this study. I understand that my child may also have to agree to participate in the study before he/she will be allowed to be in this study. I have read this form, or have had it read to me in a language that I understand. I have been given enough time to make this decision. I have asked questions and received answers about things I did not understand. I willingly give permission for my child to participate in this study. By signing this form, I am not giving up any rights to which I am entitled under law.

I understand that:

- I can withdraw permission for participation in this study and for the use and/or disclosure of PHI by contacting the person in charge of the study listed on the first page of this form.
- The use and/or disclosure of my child’s PHI will stop after Nemours receives the withdrawal notice. Information that is used or disclosed before the withdrawal may still be used.
- My child’s PHI may be disclosed again by the person or organization (other than Nemours) that receives it. If this happens, Federal or state law may not protect the information.
- I have the right to refuse to sign this permission form.
- If I refuse to sign this permission form, my child will not be allowed to be in this research study.
- I have the right to ask Nemours to tell me who has received my child’s protected health information.
- I have the right to revoke my permission for the use and disclosure of my child’s health information at any time, which would end his/her participation in this study.
- I will receive a signed and dated copy of this form.

My signature indicates that:

- As his or her parent or guardian, I give my permission for the minor child named below to participate in the research study described in this Parental Permission Form.
- I give the researchers and Nemours permission to use and/or disclose my child’s individually identifiable health information for this research study as described in Section 19.

Name of Participant (Print)

Participant Date of Birth:

Signature of Parent / Guardian

Printed Name of Parent / Guardian

Date

Check Relation to Participant: Parent Guardian: (Guardians must have documented authority to give permission for participation in a research study according to the laws of the State in which the treatment occurs.)

I the undersigned, certify that to the best of my knowledge the parent/legal representative signing this permission had the study fully and carefully explained and that he/she understands the nature, risks and benefits of participation in this research study.

Name of Person Obtaining permission (Investigator or Designee)

Signature of Person Obtaining permission

Date

Copy of the signed form was provided to Participant on [Date] _____