CONSENT TO PARTICIPATE IN A RESEARCH STUDY FOR AN ADULT
INFORMED CONSENT - PART I

Title of Study: **Tissue selective estrogen complex to prevent metabolic dysfunction in women (RISE)**

What you should know about a research study

- We give you this consent form so that you may read about the purpose, risks and benefits of this research study.
- The main goal of research studies is to gain knowledge that may help future participants.
- You have the right to refuse to take part, or agree to take part now and change your mind later on.
- Please review this consent form carefully and ask any questions before you make a decision.
- Your participation is voluntary.
- By signing this consent form, you agree to participate in the study as it is described.

1- Who is doing the study?

Investigator Information:

Principal Investigator:	Eric Ravussin, Ph.D. 225-763-3186
Co-Principal Investigator:	Franck Mauvais-Jarvis, M.D., Ph.D. 504-988-5990
Medical Investigators:	Frank Greenway, M.D. 225-763-2576 24-hr. Emergency Phone Nos.: 225-763-2500 (Weekdays 7:00 a.m.-4:30 p.m.) 225-765-4644 (After 4:30 p.m. and Weekends)

Dr. Eric Ravussin directs this study, which is under the medical supervision of Dr. Frank Greenway. We expect up to 10 post-menopausal women to complete this study at the Pennington Biomedical Research Center. The study will take place over a period of about 1-2 years. Your expected time in this study will be about 26 weeks (2-week screening period followed by two 8-week treatment periods with 8 weeks in between).

2- Where is the study being conducted?

This study takes place at Pennington Biomedical Research Center.

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3- What is the purpose of this study?

The purpose of this study is to find out if a novel drug approved by the Food and Drug Administration [Duavee™, Pfizer, Inc.] for treatment of postmenopausal symptoms (vaginal dryness and hot flashes) and prevention of osteoporosis also improves insulin sensitivity by decreasing body fat especially in your liver. You will be receiving a clinical image of the commercial drug, made specifically for this study, TSEC or a placebo.

The TSEC (Conjugated Estrogens/Bazedoxifene) is a new prescription medicine that contains a mixture of estrogen (the main female hormone made by the ovaries) and bazedoxifene, which is FDA approved. For over 60 years, estrogens have been used as hormonal treatments to help manage hot flashes and help prevent postmenopausal bone loss. But in the treatment of postmenopausal women, the use of estrogens alone can increase the risk of developing cancer of the uterus. So estrogens have been traditionally paired with a progestin to decrease the risk of hyperplasia (the thickening of the lining of the uterus), which can be a precursor to cancer. A TSEC drug uses bazedoxifene, a selective estrogen receptor modulator (SERM), in place of a progestin to help protect the uterus against thickening of the uterus that may result from estrogens alone.

In this study, you will get either a TSEC or the placebo (a "dummy pill" that may look like medicine but contains no active medication) first and then switch to the other pill.

4- Who is eligible to participate in the study?

Inclusion Criteria

- Post-menopausal women but less than 5 years since last period
- 50-60 years of age
- Symptomatic (hot flashes, vaginal dryness) or asymptomatic for menopause
- BMI 30-40 kg/m^2
- Normal mammogram past 12 months
- Physician clearance (Ob/Gyn, Baton Rouge General Physician Primary Care Network or PBRC)
- Be willing to accept your own blood during an IV procedure

Exclusion Criteria.

- Amenorrhea other causes (excess androgen)
- Diabetes mellitus
- Medications: (diabetes, antipsychotics, oral steroids, weight loss drugs†)
- History of major depressive episodes requiring treatment
- Tricyclic antidepressants (TCAs)
- Current smokers, or having smoked within last 3 months
- ≤ 3 month washout of birth control pill, estrogen, and/or progestin
- Hysterectomy (total and partial)
- Contraindications to estrogen treatment††
- Unable or unwilling to do an MRS
- Additional exclusion for optional BIA procedure only:
  - Medications: Diuretics, glitazones
  - Congestive heart failure
  - Chronic kidney disease

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- Pacemaker or other metal implants

†other chronic medications are acceptable as long as stable for 2 months, and may need MI approval before screening.†† for unusual vaginal bleeding, blood clots, hepatic disease, bleeding disorder, past/present history of breast or uterine cancer, pregnant, breastfeeding

5- What will happen to you if you take part in the study?

Summary

This study involves a screening process to see if you are eligible to participate followed by two 8-week treatment periods separated by an 8-week washout period. The two 8-week treatments will be with:

a) 8 weeks of treatment with *TSEC (combination of CE and BZA)* 8 weeks of treatment with a "dummy pill" *(Placebo)*

The order of these 2 8-week treatment periods will be decided by chance (coin flip).

STUDY VISITS (11 VISITS in total)

If you participate in this study, you will complete 1 screening visit at Pennington Biomedical Research Center to determine your eligibility. If you are eligible and enrolled in the study, you will complete an additional 10 visits (8 brief visits and 2 overnight inpatient stays).

Please note all times provided for procedures and the total times for each clinic visit are approximations and may vary depending on circumstances.

SCREENING VISIT (1 visit, approximately 2.5 hour) – FASTING Visit: Please do not drink any food or water for 10 hours before this appointment

We ask you to report to the Pennington clinic fasting. After a detailed explanation of the whole study by a coordinator, if you agree to the procedures by signing a consent form, you will have:

1) Your height and body weight measured.
2) You will then have an ECG (electrocardiogram) to measure your heart rate and rhythm.
3) Your blood pressure will be measured.
4) A blood sample (~ 2 teaspoons) and urine will be collected to assess your general health.
5) You will have a medical history and physical examination.

If fully eligible according to the data collected during the screening visit, you will be called to set up a second visit to provide you with the medication or the dummy pill.

VISIT 2 and 7 (30 minutes) – NON-FASTING

You will come to Pennington to pick up your drug supply (real medication or dummy pill) and meet with a nurse or a study coordinator to give you instructions on when and how to take your pill once a day.

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VISITS 3-5 and 8-10 (30 minutes each) – NON-FASTING

At week 1, 3 and 5 of your 8-week treatment period, you will come to our outpatient clinic to measure your weight, blood pressure and pulse, collect some feedback on your health and check your medication compliance as well as distribute new medications.

VISIT 6 and 11 (24 hours at our inpatient unit)

You will be admitted to our inpatient unit at 4pm (not fasted) for measures of:

1) Total body fat by dual-enegy X-ray absorptiometry (DXA)
2) Abdominal visceral fat by Magnetic Resonance Imaging (MRI)
3) Fat in your liver and muscle by Magnetic Resonance Spectroscopy (MRS)

You will then receive a standard dinner at ~7pm and will be ask to switch off the light in your bedroom at ~10pm.

The next morning we will wake you up at ~4.45am to be weighed and to start an IV line and start an 8-hour procedure (Euglycemic Clamp) to measure how your body responds to insulin. Also during this procedure, you will have muscle and fat biopsies, as well as possibly have bioelectrical impedance analysis (BIA) performed to assess body fluid volumes and body composition (optional procedure). You will be discharged from the inpatient unit between 2pm and 3pm after being fed a lunch.

Procedure	**Visits**					
	1	2 & 7	3 & 8	4 & 9	5 & 10	6 & 11
	Screening	Wk0 & 17	Wk1 & 18	Wk3 & 20	Wk5 & 22	Wk8 & 25
ECG	X					
Vital Signs, Height[1], Weight, Waist & Hip Measurements	X		X	X	X	X
Fasting Blood & Urine Sample	X					X
Medical History & Physical Exam + Questionnaire Barriers	X					
Pick up pills/receive instructions		X	X	X	X	
Health Status/Medication Compliance			X	X	X	X
Admittance to Inpatient Unit						X
Body Composition (DXA)						X
Body Composition (MRI)						X
Liver/Muscle Fat (MRS)						X
Euglycemic Clamp w/ RMR						X
Muscle and Fat biopsies						X
Bioelectrical Impedance Analysis (BIA) (optional)						X

1: Height will only be measured at Screening (Visit 1).

Eight weeks later (during which you will not take any pill), you will start the same sequence of visits **(VISITS 7-11)** as shown above for Visits 2-6 but this time with the other pill.

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DESCRIPTION OF PROCEDURES

Euglycemic IV clamp: 8 hours
This procedure measures how the body responds to insulin. Insulin is normally produced by your body during meals and helps your body use sugar. During the procedure about 4 tablespoons of blood will be collected. There will be 2 IV lines, one in your arm and one in your hand on the opposite side. Approximately 30 minutes after the IV lines are inserted, we will perform a fat biopsy to sample fat cells beneath the skin of your stomach area. Then, a muscle biopsy will be obtained to sample muscle cells beneath the skin of your thigh. Small amounts of glucose and insulin will be infused into your arm. Your blood sugar level will be checked every 5-10 minutes from the IV in your hand to determine how much glucose you should have to keep your blood sugar at a normal level. Your hand will be placed inside a warming box to increase skin temperature to about 105 degrees Fahrenheit. The temperature will be warm, but not uncomfortable. **During your IV procedure, a small amount of your own blood (less than 1 teaspoon) will immediately be returned into your vein through the IV after each specimen is collected.**

RMR (Resting Metabolic Rate)
Three times during the 8-hour procedure described above, we will place a clear plastic hood, through which fresh air flows, over your head to measure how many calories your body burns. This measure will last 40 minutes each time. Your urine will be collected throughout the test in a urine jug (at the end of the test or in 2 collections if necessary).

Fat biopsy: about 30 minutes Fast for 10 hours before the test
This procedure is used to sample fat cells from underneath the abdominal skin after cleansing the skin with iodine and using a local anesthetic. After cleansing the area, the doctor, nurse practitioner, or Physician Assistant will make a small incision in the skin and introduce a needle under the skin to remove fat cells. About 1 gram (less than half a teaspoon size) of fat will be removed. After the biopsy is completed, the skin will be held closed with a sterile adhesive bandage; an antibiotic ointment will be applied.

Muscle Biopsy: about 30 minutes Fast for 10 hours before the test
This procedure is used to sample muscle cells from underneath the skin of the leg. After cleaning the skin with iodine and using a local anesthetic, the doctor, Nurse Practitioner, Physician Assistant will make a small incision in the skin and introduce a needle under the skin to remove muscle cells. About 200-750 milligrams (less than a teaspoon size) of muscle will be removed. After the biopsy is completed, the skin will be held closed with a sterile adhesive bandage and an antibiotic ointment will be applied.

Bioelectrical Impedance Analysis (BIA) Measurements: about 10 minutes – Optional Procedure

This procedure is used to sample body fluid volumes and body composition. You will be asked to change into a gown and to remove all footwear and socks/stockings. Once changed and barefoot, you will be asked to empty your bladder and to have your weight measured. Then, you will be asked to lie down for 10 minutes. Your skin will be cleaned

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with disinfectant wipes, and two pairs of disposable electrodes will be placed on your right hand and your right foot where the skin was disinfected. Two cables will be connected to the electrodes, and the bioelectrical impedance analysis will be performed.

DXA - Whole Body Scan: ~10 minutes

This scan measures the amount of bone, muscle, and fat in your body. The scan will be performed using a whole-body scanner. You will be required to wear a hospital gown, to remove all metal-containing objects from your body, and to lie down on the table. A scanner emitting low energy X-rays and a detector will pass along your body. You will be asked to remain completely still while the scan is in progress. The scan takes less than four minutes. This scan is for research purposes only and not for diagnostic treatment.

MRI Abdomen: 30 minutes

This scan measures the amount of fat in your abdomen. You will change into a hospital gown and remove all objects containing metal from your body. You will lie on your back on the scanner table with your arms above your head. A large coil will be placed around your upper abdomen. You will then be moved into the magnet and will be instructed to hold your breath 4-5 times (once for six seconds, once for 13 seconds, and 2-3 times for about 18 seconds After the upper abdominal scans are completed, you will be moved up on the table, and the coil will be placed over your lower abdomen. The same scans will be acquired over this area with the same 4-5 breath holds. The total scan time for this procedure is approximately 30 minutes. During the scan, you will hear loud tapping noises. You will be given headphones for protection from the scanner noise and can listen to music during the scan if desired. You will also be given a call button should you need the MRI Technician during the exam. This scan is for research purposes only and not for diagnostic treatment.

MRS IHL (Intrahepatic lipid): 20-30 minutes

This scan measures the amount of fat in your liver. You will change into a hospital gown and remove all objects containing metal from your body. You will be placed on the scanner table head first and on your stomach. The table will move you into the magnet where data will be obtained. The scan will last for approximately 20-30 minutes. During the scan, you will hear loud tapping noises. You will be given head phones for protection from the scanner noise and can listen to music during the scan if desired. You will also be given a call button should you need the MRI tech during the exam. This scan is for research purposes only and not for diagnostic treatment.

MRS IMCL (Intramyocellular lipid): 60 minutes

This scan measures the amount of fat in your muscle fibers. You will change into a hospital gown and remove all objects containing metal from your body. You will lie on your back on the scanner table with the right leg in a special coil. The top part of the coil will then be placed over your calf. Cushions will be inserted around the calf to help keep the leg as still as possible. The table will then move you into the scanner where a series of several scans will be obtained. The entire procedure will last approximately 60 minutes. During the scan, you will hear loud tapping noises. You will be given head

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phones for protection from the scanner noise and can listen to music during the scan if desired. You will also be given a call button should you need the MRI tech during the exam. This scan is for research purposes only and not for diagnostic treatment.

6- What are the possible risks and discomforts?

- Risks associated with a TSEC (Bazedoxifene/Conjugated Estrogens (BZA/CE). The most common side effects reported in at least 1 out of 100 postmenopausal women receiving BZA/CE include abdominal (stomach) pain, vaginal discharge, vaginal yeast infection, and leg cramps. Other adverse events reported in less than 1 out of 100 subjects were gall bladder disease and increase in liver function tests. More serious but rare side effects associated with the use of BZA/CE included venous thromboembolic events (blood clot in a vein of the legs or lungs), reported in less than 1 out of 100 subjects. If you experience sudden pain in legs or difficulty breathing, **notify the Medical Investigator immediately**.

Precautions
You may be allergic to conjugated estrogens or bazedoxifene. If you experience allergy symptoms such as rash, hives, or itching, **notify your study doctor immediately**.

All estrogens and SERMS should be stopped prior to and during prolonged immobilization (such as bed rest, surgery or long-distance travel). It is recommended that study drug be discontinued 1 week prior to prolonged immobilization (orthopedic surgeries or flights > 8 hours. **As with any planned discontinuation of medications, please contact the study investigator or coordinator prior to any surgeries or extended flights.**

You may not use hormone products during the study; including any oral, transdermal, vaginal or other products containing estrogens, progestins, androgens, testosterone, DHEA or SERMs.

- **Blood Draws:** There is the possibility of infection and/or pain and bruising at the site where the needle is inserted. Aseptic (sterile) technique and trained personnel minimize these risks.

- **DXA:** The amount of radiation used for this procedure is very small. The radiation dose for a DXA scan is equivalent to the radiation you are naturally exposed to in the environment in less than one day.

- **MRI & MRS:** There is a small chance of claustrophobia or muscle-skeletal discomfort from lying partially in the magnet. During the imaging measurement, the noise may be somewhat unpleasant, but your headphones will help with this. Although the long-term risk of exposure to a magnetic field is not known, the possibility of any long-term risk is extremely low from the information accumulated over the past ten years.

MRI/MRS Warning: Certain implants, devices, or foreign objects implanted in the human body may interfere with the MR procedure. Volunteers who have undergone specific prior surgeries (i.e. heart, brain, gastric bypass, breast augmentation, etc.) and/or have implants of specific types may be required to provide their IMPLANT CARD in order to determine implant safety/compatibility with the magnet before a scan is performed.

- **Two-Step Clamp Procedure:** There is a possibility of pain, bruising, or infection at the site of the needle insertion for the IV line. Trained personnel minimize this risk. There is a small risk of developing low blood sugar. If this happens it can make you feel hungry and your heart may beat faster. If not treated, low blood sugar can cause coma, seizures, and even death. Precautions are taken to avoid low blood sugar: A doctor will be present on site and a registered nurse will be available at all times during the clamp. Your blood sugar will be measured every 5-10 minutes, and dextrose (a sugar) will be administered intravenously as needed to prevent a drop in blood sugar levels. **If your blood sugar drops to a level considered unsafe, the procedure will be stopped immediately and dextrose will be given through the IV line.**

- **RMR:** There is no known risk in having a RMR (resting metabolic rate). If you are claustrophobic, it may be uncomfortable to have the plastic hood over your upper body.

- **Fat Biopsy:** Mild to severe pain, soreness, and bruising, and a small scar are common risks. There is a small risk of a hematoma (collection of blood in the tissue) or infection at the biopsy site. Sterile technique will be used to minimize these risks and the biopsy site will be monitored closely.

- **Muscle Biopsy:** Mild to severe pain, soreness, bruising, and a small scar are common risks. A hematoma (collection of blood in the tissue) may occur. There is a slight risk that a superficial nerve may be cut; the nerve may heal, or it may result in a permanent loss of sensation in the skin at the biopsy site.

- **Bioelectrical Impedance Analysis (BIA): Measurements will not be performed on any subject who is pregnant, and all females should inform the technologist if there is any possibility that they are pregnant**. There is no risk associated with the BIA measurement. **However, subjects with medical implants such as a pacemaker or metal joint replacements cannot be measured on the machine.**

In addition to the risks listed above, you may experience a previously unknown risk or side effect.

7- What are the possible benefits?

We cannot promise any benefits from your being in the study. However, possible benefits include learning about your health.

8- If you do not want to take part in the study, are there other choices?

You have the choice at any time not to participate in this research study. If you choose not to participate, any health benefits to which you are entitled will not be affected in any way.

9- If you have any questions or problems, whom can you call?

If you have any questions about your rights as a research volunteer, you should call the Institutional Review Board Office at 225-763-2693 or the Executive Director of Pennington Biomedical at 225-763-2513. If you have any questions about the research study, contact Dr. Eric Ravussin at 225-763-3186. If you think you have a research-related injury or medical illness, you should call Dr. Frank Greenway at 225-763-2576 during regular working hours. After working hours and on weekends you should call the answering service at 225-765-4644. The on-call physician will respond to your call.

10- What information will be kept private?

Every effort will be made to maintain the confidentiality of your study records. However, someone from Pennington Biomedical Research Center or Tulane University may inspect and/or copy the medical records related to the study. Results of the study may be published; however, we will keep your name and other identifying information private. Other than as set forth above, your identity will remain confidential unless disclosure is required by law.

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.

11- Can your taking part in the study end early?

Dr. Eric Ravussin, Dr. Frank Greenway, or the study sponsor can withdraw you from the study for any reason or for no reason. You may withdraw from the study at any time without penalty; however, all data Pennington Biomedical has previously collected cannot be removed from the study. Possible reasons for withdrawal include not following the study requirements. The sponsor of the study may end the study early.

12- What if information becomes available that might affect your decision to stay in the study?

During the course of this study there may be new findings from this or other research which may affect your willingness to continue participation. Information concerning any such new findings will be provided to you.

13- What charges will you have to pay? None.

14- What payment will you receive?

If you agree to take part, we will pay you $1000 if you complete the entire study. A first check of $350 will be requested from the LSU payroll department after completing the first 8-week treatment period and a second check of $650 will be requested when you complete the study. It usually takes about 3-4 weeks for it to arrive at Pennington Biomedical Research Center.

15- Will you be compensated for a study-related injury or medical illness?

No form of compensation for medical treatment or for other damages (i.e., lost wages, time lost from work, etc.) is available from the Pennington Biomedical Research Center. In the event of injury or medical illness resulting from the research procedures in which you participate, you will be referred to a treatment facility. Medical treatment may be provided at your expense or at the expense of your health care insurer (e.g., Medicare, Medicaid, Blue Cross-Blue Shield, Dental Insurer, etc.) which may or may not provide coverage. The Pennington Biomedical Research Center is a research facility and provides medical treatment only as part of research protocols. Should you require ongoing medical treatments, they must be provided by community physicians and hospitals.

16- Storage of Blood for Future Research or Use

Biospecimens for future research:

You are being asked to allow some of your blood to be stored and used for research at a later time. These bodily materials are called biospecimens. The donation of biospecimens in this study is optional. No matter what you decide to do, it will not affect your study participation. You will still be allowed to take part in the study even if you don't want your specimens to be collected and used for future research. Some biospecimen samples will be stored and used for the study and other biospecimen samples will be stored for future studies. The collection of samples may give scientists valuable research material that can help them to develop new diagnostic tests, new treatments, and new ways to prevent diseases. If you agree to have your samples stored, you can change your mind later.

The samples will be stored indefinitely. If you agree to donate your samples, they may be given to other investigators for future research as well. The future research may take place at Pennington Biomedical and may involve Pennington Biomedical Researchers in this study. The future research may not take place at Pennington Biomedical Research Center and may not be reviewed by Pennington Biomedical Research Center's Institutional Review Board. For privacy and confidentiality, your biospecimens will be labeled with a unique series of letters and numbers. Pennington Biomedical will store your biospecimens with this unique identifier and the minimum number of personal identifiers to meet laboratory standards. The research done with your specimens may help to develop new products in the future, or may be used to establish a cell line or test that could be patented or licensed. You will not receive any financial compensation for any patents, inventions or licenses developed from this research.

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Making your choice about future research:
Please read about each biospecimen below. It is your choice which samples will be collected, stored and used for future research for this study or future studies. After reading about each below, sign next to "Yes" or "No" to show your choice about the collections for this research study and for future research studies.

Blood
If you give permission, approximately 6 tablespoons of blood will be collected and stored by this study. Your stored samples may be tested at Pennington Biomedical Research Center or other locations used in future research. Do you give permission for your blood to be collected and used in future research by this study?

Yes, I give permission _____ _____
Signature Date

No, I do not give permission _____ _____
Signature Date

Tissue
If you give permission, your left over tissue, tissue not be used for the purposes of the current study will be collected and stored by this study. Your stored samples may be tested at Pennington Biomedical Research Center or other locations used in future research. Do you give permission for your tissue to be collected and used for future research?

Yes, I give permission _____ _____
Signature Date

No, I do not give permission _____ _____
Signature Date

Making your choice about additional procedures:

BIA
If you give permission, the data collected from the BIA procedure will be used in future research. Do you give permission for your data to be collected and used for future research?

Yes, I give permission _____ _____
Signature Date

No, I do not give permission _____ _____
Signature Date

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17- Signatures

The study has been discussed with me and all my questions have been answered. I understand that additional questions regarding the study should be directed to the study investigators. I agree with the terms above and acknowledge that I have been given a copy of the signed consent form.

With my signature, I also acknowledge that I have been given either today or in the past a copy of the Notice of Privacy Practices for Protected Health Information.

_____
Printed Name of Volunteer

_____ _____
Signature of Volunteer Date

_____
Date of Birth of Volunteer

_____ _____
Signature of Person Administering Informed Consent Date

Eric Ravussin, Ph.D.
Principal Investigator

Frank Greenway, M.D.
Medical Investigator