CEDARS-SINAI MEDICAL CENTER

CONSENT FORM FOR RESEARCH

Title: Treatment of pituitary Cushing disease with a selective CDK inhibitor, R-roscovitine

STUDY SUPPORT PROVIDED BY: NATIONAL INSTITUTES OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES (NIDDK)

PARTICIPATING RESEARCHERS:

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STUDY CONTACT PHONE NUMBER AT CSMC: 310-423-2830

AFTER HOURS CONTACT (24 HOURS): 310-423-5000

This research study is sponsored by the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK). Additionally, Cyclacel Pharmaceuticals, Inc. is also providing support for the conduct of this research.

1. WHAT IS THE PURPOSE OF THIS RESEARCH STUDY?

We are doing this study to evaluate the effectiveness and safety of R-roscovitine (seliciclib) in people who have rare tumors of neuroendocrine origin (such as the tumors of the pituitary gland). This research study is designed to find out if R-roscovitine is safe and has beneficial effects. In this study, we want to learn what effects, good or bad, R-roscovitine has on people with your condition. We will give R-roscovitine to research participants and watch carefully for any side effects.

This research study is designed to test the investigational use of R-roscovitine. This drug has not yet been approved by the U.S. Food and Drug Administration (FDA). R-roscovitine is a so called cyclin-dependent kinase (CDK) inhibitor that modifies the growth phase or state of a cell while it is being treated. R-roscovitine shows potential therapeutic use in directly targeting human ACTH production.

You are being asked to take part in this research study because you have Cushing's disease, a pituitary tumor of rare endocrine origin (such as a prolactinoma, non-functioning adenoma, TSH-secreting adenoma, or an ectopic ACTH-secreting adenoma) are newly diagnosed, or you have not responded to standard therapy or there is no treatment available to you. This is caused by over production of adrenocorticotropic hormone (ACTH) by a noncancerous tumor of the pituitary gland. The pituitary gland is an organ located at the base of the brain that produces hormones. Hormones are chemicals in the body that direct biological activities. Over production of the pituitary hormone, ACTH, can lead to

excessive levels of cortisol in the body and Cushing's disease. Cortisol is also a hormone, and its release in the body leads to an increase in blood sugar levels.

The study will enroll up to 16 participants in total.

2. WHAT WILL HAPPEN DURING THE STUDY?

This section provides a general overview of what will happen during your participation in this study. Information included below should be considered along with the flowchart of procedures attached as Appendix A.

The flowchart shows a timeline for research-related or standard of care procedures that are involved in your participation in this study. **Research-related procedures** are those performed solely for the research. They would not be performed if you did not take part in the study. **Standard of care (routine)** procedures would be performed both as part of this study and if you do not participate in this study.

A table describing common medical procedures done solely for the purposes of monitoring and assessing your condition during this study is attached as Appendix B to the end of this consent form. Standard of care procedures that will be repeated or done at greater frequency are listed in the flow chart, attached Appendix A.

Overview of study:

During the study, you will receive R-roscovitine 400 mg oral administration twice daily for 4 days every week for a total of 4 weeks. The dose of R-roscovitine could be reduced by 25% if you are unable to tolerate the protocol specified dosage, and/or the investigator believes that an ongoing drug-related adverse reaction is present.

Washout:
This study requires you to stop taking other drugs for 2 weeks so they may be flushed from your body in order to prevent conflicts with the study drug. For this study, you are required to stop taking metyrapone, ketoconazole, pasireotide, mifepristone, and CYP3A4 inducers or inhibitors for 2 weeks. In addition, you will also be required to discontinue cabergoline for 4 weeks. Consult with the researchers before taking any non-study medications including over-the-counter drugs or vitamins. Possible risks from the washout are discussed in the section "What are the Possible Risks or Discomforts?"

Visual Field Exam:
A visual field exam measures all areas of your eyesight. During this procedure you will look inside a bowl-shaped instrument called a perimeter. You will stare at the center of the bowl and lights will flash. You will be instructed to press a button each time you see a flash. At the end of the procedure, a printout will show if there are areas where you did not see the flashes of light and these are areas of vision loss.

24 Hour Urine Collection
You will receive a 4L container on visit 1A. You will start collecting your urine in the morning. You will empty your bladder first thing in the morning but do not save this urine. Mark down the time that you urinated because that will be the beginning of you 24-hour collection period. For the next 24 hours, collect all your urine. You will be instructed to bring the container back the next day.

Blood Collection every 3 hours for 6 hours
You will return for the baseline visit 7-9 days after the screening visit. Plasma ACTH (adrenocorticotropic hormone) and serum cortisol levels will be collected every 3 hours from 9:00 AM – 3:00 PM. There will be a total of 5 blood draws during this time. In the even that an intravenous catheter cannot be placed, one blood draw will be performed every three hours. Measuring ACTH and cortisol in the blood helps physicians detect diseases that are associated with cortisol, such as Cushing's disease. Testing the levels of ACTH and serum cortisol is done by using a blood sample with the use of an IV catheter so that we will not have to stick you every 2 hours. A blood sample will be taken from your vein, usually from the inside of your elbow. An elastic band will be tied around your arm to cause the vein to swell with blood and a needle syringe is inserted into the vein to collect the blood. This collection of blood every 3 hours from 9:00 AM – 3:00 PM will take place at Baseline (Day 0), Day 1, 8, 15, 22, and 29 visits.

Dexamethasone Suppression Test:
Dexamethasone will be dispensed during the screening visit. Study doctor will explain when the subject should take it. During an overnight dexamethasone suppression test, you will take 8mg of dexamethasone orally the night before at 11:00 PM at home. You will come into the clinic for your baseline visit the next morning and will have blood drawn between 8:00 AM - 9:00 AM to test their serum cortisol levels. Dexamethasone, which acts like a cortisol, decreases the amount of ACTH released by the pituitary gland, which then decreases the amount of cortisol released by the adrenal glands. After taking a dose of dexamethasone, cortisol levels often stay abnormally high in people who have Cushing's syndrome. This procedure will confirm the diagnosis of Cushing's disease.

If you have previously undergone a dexamethasone suppression test at Cedars-Sinai Medical Center, you will not need to repeat the same test. You will not be required to undergo this test if your diagnosis has been previously confirmed via previous surgery or IPSS as it would not be necessary to re-confirm your diagnosis.

Saliva Collection:
You will be asked to provide saliva samples which will be collected to measure elevated late evening cortisol. A swab will be placed directly into your mouth for 2 minutes. You will roll the swab around your mouth. You will be instructed not to touch the swab with your fingers or chew the swab. You will be asked to do this at Visits 1-6.

Other Medications: During your participation in this study, it is very important that you notify the study doctor what medications you are currently receiving or have received in the recent past. It is also very important that you notify the study doctor or nurses before you take any new medications during the course of the study, including any changes to your current medications as they may have interactions with the study drug. Grapefruit juice should be avoided while you are taking r-roscovitine.

Length of participation

We think you will be in this study for about a month. The total time includes 8 study visits.

Participation of Individuals Travelling to Cedars-Sinai from International Sites
Cedars Sinai has opened participation in this trial to individuals identified and referred for participation by hospitals or physicians in other countries. International participants will be required to travel to Cedars-Sinai for participation in the study, and remain in California for the duration of study participation. Additional information related to requirements for international participants travelling to Cedars Sinai for this study is detailed in an appendix to this consent form.

3. WHAT ARE THE POSSIBLE RISKS?

Risks of common medical procedures performed solely for research purposes are described in a table attached to the end of this consent form as Appendix B. Side effects and risks of standard of care procedures are not described in this consent form.

This section describes the possible risks and/or discomforts we anticipate you could experience that are related to the study procedures:

Risks of R-roscovitine (Seliciclib):

Commonly reported side effects of r-roscovitine seen in clinical trials include:

- Fatigue
- Nausea
- Vomiting
- Decreased appetite
- Elevation in liver enzymes (which may indicate liver dysfunction)
- Elevated blood creatinine levels (which may indicate kidney dysfunction)
- Hypokalemia (low potassium levels)
- Anemia (low red blood cell counts that can cause tiredness or fatigue; may require a blood transfusion)

Most of these were mild to moderate side effects and were reversible after discontinuation of drug. Other less common side effects seen include:

- Fever
- Stomach pain
- Changes in blood sugar level
- Difficulty sleeping
- Rash

Risks of Dexamethasone:

Common, some may be serious (occurs in	**Occasional, some may be serious** (occurs in 10-25%	**Rare, and serious** (occurs in 1-9% of	**Possible, some may be serious** (occurs in

greater than 25% of people)	of people)	people)	less than 1% of people)
• Fatigue • Nausea • Vomiting	• Fever • Abdominal pain • Increased appetite	• Rash • Itching/swelling especially of the tongue/face/throat • Dizziness • Trouble breathing	• Mental/mood swings • Unusual hair/skin growth • Muscle pain/cramps • Easy bruising/bleeding • Insomnia • Bone/joint pain • Vision problems

Reproductive and Lactation Risks
Taking part in this research study can affect an unborn baby. Therefore, you should not become pregnant or father a baby while on this study. If you or your partner is capable of becoming pregnant you will need to use birth control. Check with the researcher about approved birth control methods to use while participating in this study.

Women should not breastfeed a baby while on this study.

Unknown Risks to the Developing Embryo or Fetus (an unborn baby)
If you are pregnant, or become pregnant during participation in this research, the study drug (R-roscovitine) might involve risks to an embryo or fetus, which are currently unknown. It is important that you contact the researcher immediately if you believe you might be pregnant.

Collection of Pregnancy Outcomes
If you become pregnant during the study, we will collect information on the outcome of your pregnancy including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, abnormalities, or complications. Thus by signing this consent, you are agreeing to have this information about you and your child collected from your medical records in the rare case that you become pregnant during your participation in this research study.

If you are a male participant and your female partner becomes pregnant during the study, we will ask your female partner for consent and authorization to collect information on the outcome of her pregnancy and the status of your child, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, abnormalities, or complications. This information will be collected from your female partner's medical records with her permission.

Risks of Discontinuation of Current Medication
In order to participate in this research study, you must stop taking any medications you are currently taking for Cushing's disease. This may result in a worsening of your condition. Any symptoms prior to medication may return. These symptoms can include increased cortisol, mood swings, hypertension, diabetes, or psychotic episodes. We will closely monitor cortisol and mood swings. As for those with

hypertension and diabetes, they will be placed on antihypertensive and diabetic medication. Those with a prior history of psychotic episodes will not be enrolled in this study.

Follow-up Visit for Discontinuing Participants
While you are free to discontinue your participation at any time, we encourage you to complete a Final Study Visit. During this visit, we will conduct tests to collect safety data, and discuss any information that may be important to share with your treating physician.

Unknown Risks
There also may be other side effects or risks that we cannot predict. Many side effects may go away shortly after the study medication or procedure is stopped. However, in some cases they can be serious, long-lasting, permanent, and/or fatal.

Incidental Findings
It is possible that the research procedures could uncover information related to your health that you did not know about before and that is unrelated to the Study. Some of these findings may be too preliminary to share. Cedars-Sinai will carefully consider the research findings and determine if they should be shared with you. Research findings would only be shared with you if such sharing is approved by the Cedars-Sinai IRB and is permitted by applicable law. In some cases, additional clinical testing may be required. The cost of any additional testing and any related treatment will be your responsibility.

4. ARE THERE BENEFITS IN TAKING PART IN THE STUDY?

If you agree to take part in this research study, there may or may not be direct medical benefit to you. The possible benefit of taking part in the research study is treatment of your tumor of rare endocrine origin when previous treatments have not been effective. However, no benefit is guaranteed. It is possible that your condition may remain unchanged or even get worse.

While no benefit is ever guaranteed, we hope the information learned from this research study will benefit other patients with inadequately controlled symptoms from rare tumors of endocrine origin in the future by helping us to learn about the safety and effectiveness of this investigational drug.

5. WHY WOULD MY PARTICIPATION BE STOPPED?

Your participation in this study may be stopped at any time by the researcher or the sponsor without your consent for any reason, including:

- The study is stopped or suspended;
- Funding for the study is reduced, stopped or withdrawn;
- If it is in your best interest;
- You do not consent to continue in the study after being told of changes in the research that may affect you;
- You do not follow the study procedures.
- Adverse event(s)
- Abnormal laboratory value(s)

- Abnormal test procedure result(s)
- Protocol violation
- Lost to follow-up
- Administrative problems
- Death

6. ARE THERE ANY OTHER OPTIONS?

Your participation is voluntary so you have the right to decline to participate or to withdraw from this research study at any time without any penalty or loss of benefits to which you would be entitled outside of the study. Choosing not to participate will not affect the care you receive at Cedars-Sinai Health System.

If you decide not to take part in this study, you have other choices. For example:

- you may choose to be treated following the usual clinical approach such as somatostatin analogues, growth hormone antagonists and dopamine agonists, which are available by prescription to treat symptoms experienced by patients with your condition
- you may choose to take part in a different study at CSMC or elsewhere, if one is available
- you could decide not to be treated.

The researcher will discuss these options and their risks and benefits with you.

7. WILL MY INFORMATION BE KEPT CONFIDENTIAL?

We will do our best to make sure that the personal information collected as part of this study is kept private. However, we cannot guarantee total privacy. A copy of your research consent and authorization forms may be filed in your electronic medical record at CSMC. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other identifiable personal information will not be used. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include: accrediting agencies, government and regulatory groups (such as Food and Drug Administration (FDA), Office for Human Research Protections (OHRP), etc.), safety monitors, companies that sponsor the study, and authorized representatives of the sponsor.

The study team will facilitate any required access to your records by authorized representatives of the Sponsor to verify the information collected for the study.

You may, depending on the circumstances of the study and applicable law, be asked to sign a separate "Authorization Form" that outlines with whom your information may be shared for the purposes of this research and under what circumstances.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at any time.

8. WHAT IF I BECOME ILL OR INJURED BECAUSE OF TAKING PART IN THIS STUDY?

Contact your researcher at once if you feel that you are ill or have been injured because of taking part in this study. If it is a medical emergency, call 911 or go to an emergency room. Promptly notify your researcher of your situation at the phone number listed on page 1 of this consent form.

Who pays for my research related illness or injury?
A research injury or illness is a direct result of the Study Drug, or a procedure performed only as a part of the study and is not part of your standard clinical medical treatment. If you are being treated for a research injury or illness, you will not pay for the costs of care provided by Cedars-Sinai Health System or in any emergency room provided that you are being treated for a research injury or illness. Cedars-Sinai may, however, ask for reimbursement where allowed from parties such as your health plan. Losses such as lost wages will not be paid. If you choose to obtain non-emergency care elsewhere, you or your health plan may be responsible for the costs of that care.

9. FINANCIAL CONSIDERATIONS

Costs of Participation
Please review the attached Appendix A flowchart for a listing of items, drugs and services that will be billed to you and/or your insurance and those that will be covered by Cedars-Sinai institutional grant.

Only items, drugs and services that are reasonable and necessary for your medical care throughout the study will be billed to your insurance. You remain responsible for all deductibles, co-pays, and balances under your health benefit plan. If your insurance company does not pay, you will be billed for those charges. You should check with your health benefit plan if you have questions or concerns about your insurance coverage.

Compensation for Participating
You will receive a $10 meal voucher at each study visit that may be used at the Cedars-Sinai Cafeteria, Plaza Café, or Starbucks Coffee on the Plaza Level of the main hospital. You will also be reimbursed for your travel (mileage) for each research study visit at the current IRS mileage reimbursement rate. If you are traveling to Los Angeles from out of town, the study team may arrange accommodations for an overnight stay on the day of your visit. You will receive reimbursement for mileage at the end of your participation in the study. If you do not complete the entire research study, you will only be reimbursed for mileage for those visits you do complete. You will not receive any other payment for participating in this study. You may be required to complete a W-9 Form in order to receive payment. The W-9 Form will be maintained by our accounting department at Cedars-Sinai. If payment in one calendar year is $600 or more, a 1099 Form will be filed with the IRS in accordance with federal tax law.

If you are a Cedars-Sinai employee, you should provide your employee identification number to the research team so that your payment can be appropriately processed through Payroll. For your own protection and to comply with tax laws, your payment for participation will be reported to the IRS together with other compensation you receive from Cedars-Sinai.

If you are a participant recruited at an international site, please review the appendix for international participants for details on payment for participation.

10. WHAT IF I HAVE QUESTIONS OR PROBLEMS?

Please contact one of the investigators listed on the first page of this form for questions or concerns about the research.

If you have questions, problems, and concerns that you want to discuss with someone who is not associated with this study, or want to offer feedback, please contact:

Cedars-Sinai Human Research Protection Program (HRPP) Phone: (310) 423-3783
Email: ResearchConcerns@cshs.org

The Cedars-Sinai HRPP has been established to protect the rights and welfare of research participants. You may also contact the Cedars-Sinai HRPP if you want to offer input or obtain information regarding the study.

11. CONSENT PROVISIONS

If you sign this form below, it means that:

(1) You have taken the time to carefully read and understand the information presented in this informed consent form; you should discuss it with others, and if appropriate seek a second opinion to make an informed decision;
(2) The information concerning the research study and its involved procedures has been fully explained to you and your questions have been answered to your satisfaction;
(3) You have received and understand all of the information you desire regarding your participation in the research study;
(4) You have considered the potential risks, any anticipated benefits and alternatives (and their relative risks and benefits) of participation;
(5) You are voluntarily agreeing to participate in this research study;
(6) You understand that you have the right to be informed of significant new findings related to this research study which may affect your willingness to continue participating in this study; and
(7) You have been provided with a copy of the "Experimental Subject's Bill of Rights", if applicable to this research study, and have been provided with an opportunity to ask questions regarding the Bill of Rights.

We will give you a copy of this signed and dated consent form and a signed copy of the Experimental Subject's Bill of Rights.

SIGNATURE BY THE PARTICIPANT:

Name of Participant (Print)	Signature of Participant	Date of Signature

SIGNATURE BY THE INVESTIGATOR:

I have personally explained the research to the participant in non-technical terms, answered all questions, and attest that he/she freely consents to participate. The participant has been provided with the Experimental Subject's Bill of Rights.

Signature of the Investigator Who Obtained Consent	Date of Signature

SIGNATURE BY THE INTERPRETER/WITNESS
(Signature of an interpreter is only required when a non-English speaking subject is consented with the assistance of an interpreter. The witness may be any person who is conversant in both English and the language of the Non-English speaking subject, such as the interpreter (the certified hospital interpreter), study staff, a family member, or other person. The witness signs the consent forms to confirm that the oral interpretation occurred.)

Signature of Interpreter/Witness	Date of Signature

CEDARS-SINAI MEDICAL CENTER

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

In accordance with California Health and Safety Code 24172, any person who is required to consent to participate as a subject in a research study involving a medical experiment or who is requested to consent on behalf of another has the right to:

1. Be informed of the nature and purpose of the experiment.

2. Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized.

3. Be given a description of any attendant discomforts and risks to the subject reasonably to be expected from the experiment.

4. Be given an explanation of any benefits to the subject reasonably to be expected from the experiment, if applicable.

5. Be given a disclosure of any appropriate alternative procedures, drugs or devices that might be advantageous to the subject, and their relative risks and benefits.

6. Be informed of the avenues of medical treatment, if any, available to the subject after the experiment if complications should arise.

7. Be given an opportunity to ask any questions concerning the experiment or the procedure involved.

8. Be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation in the medical experiment without prejudice.

9. Be given a copy of any signed and dated written consent form used in relation to the experiment.

10. Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject's decision.

_____ _____

Signature of Experimental Subject **Date**

Distribution instruction for researchers:

The signed (i) Consent form, (ii) Authorization for Use and Disclosure of Identifiable Health Information and (iii) "Experimental Subject's Bill of Rights" (the latter required if the research study involves medical interventions)* should be distributed to:

1) Medical Chart
2) Research Participant
3) Pharmacy (if a drug study)
4) Principal Investigator's research records (original)

FLOWCHART OF PROCEDURES

Procedures	Screening Visit -60 to -1 days before baseline	Visit 1 Baseline Day 0	Visit 2 Day 1	Visit 3 Day 8	Visit 4 Day 15	Visit 5 Day 22	Visit 6 Day 29	Study Completion Visit
Standard of Care Procedures: Items, drugs and services that are part of regular care and would be done even if you did not take part in this research study. These will be billed to you and/or your insurance company.								
Visual Field Exam	X[1]							
MRI of the Pituitary	X[2]							
Research Related Procedures: Items, drugs and services done for research purposes only. These will be covered by the sponsor of the study and will NOT be billed to your insurance company.								
Review of medical records	X							
History and Physical Exam	X		X	X	X	X	X	X
Blood Draw for blood count with differential, chemistry, liver function test and fasting lipid profile; hormone profile		X	X	X	X	X	X	X
Dexamethasone dispensed[3]	X							
Urinalysis	X						X	
Electrocardiogram (ECG)	X		X	X	X	X	X	X
24 hour Urine Collection for free cortisol	X[4]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	
Visual Field Exam			X	X	X	X	X	
Insertion of IV catheter peripherally for repeated blood draws		X	X	X	X	X	X	
Plasma ACTH and serum cortisol (Blood collection every 3 hours from 9AM to 12PM with catheter)	X[6]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	
MRI of the Pituitary							X	
Saliva sample for salivary cortisol		X	X	X	X	X	X	
Fasting lipid profile		X					X	
Pregnancy Test (for female of childbearing potential)[1]		X	X	X	X	X	X	
Study drug dispensed[8]			X	X	X	X		
Adverse events assessment			X	X	X	X	X	X

[1] Serum pregnancy test rather than urine pregnancy will be performed. Blood will be drawn during other blood collection during the participant's baseline visit.

1. If previously performed greater than 28 days from start of therapy, repeat exam will be RES.
2. If previously performed greater than 28 days from start of therapy, repeat exam will be RES.
3. Dexamethasone is taken one time the night of the screening visit. If previously performed at Cedars-Sinai Medical Center, or if the subject has been confirmed with diagnosis such as previous surgery or IPSS repeat exam is not required.
4. 2 - 24 hour UFC can be collected anytime between one week after taking dexamethasone and the baseline visit.
5. 3 - 24 hour UFC will be collected for 3 days prior to coming in for study visit.
6. Blood draws will be done only for cortisol level between 8:00-9:00 AM on the day of screening visit, and 8:00-9:00 AM the next day after 8 mg dexamethasone
7. Blood draws will be done via intravenous catheter every 3 hours from 9AM to 3PM. In the case that an intravenous catheter cannot be placed, one blood draw will be performed at every 3 hour interval.
8. Study drug is taken orally twice per day for 4 days each week.

APPENDIX B: Detailed Description of Common Medical Procedures Performed for Research Purposes and Associated Risks

The procedures listed below are often performed as part of routine care for a person with your condition. They are being repeated, or performed more frequently as part of this research. However, the risks associated with each procedure should be comparable to what you would experience even if you were undergoing the procedure outside this research study.

Study Procedure	Related Risks
Blood draw via intravenous catheter: A needle with a plastic tube attached will be inserted into a vein in your arm. This is known as an intravenous line or "IV". The samples of blood taken from the blood draw will be used to measure levels of plasma ACTH and serum cortisol.	Risks associated with having an IV placed or blood drawn, may include mild discomfort, bruising, bleeding, blood clot and a very slight risk of infection at the needle puncture site. Some people who have needle punctures may become lightheaded, nauseous or faint.
Electrocardiogram (ECG): abbreviated as EKG or ECG – is a test that measures the electrical activity of the heartbeat using electrodes (disposable adhesive discs placed on the skin).	There's no pain or risk associated with having an electrocardiogram. When the disposable adhesive discs are removed from your skin, there may be some minor skin discomfort or irritation. You may experience temporary discomfort (pulling on the skin/skin hair) during removal of the patches. This hair may be shaved for patch placement.
Magnetic Resonance Imaging (MRI): A MRI is a test that uses a magnetic field and pulses of radio wave energy to make pictures of organs and structures inside the body. During the procedure you will lie down in a large donut-like looking magnet and we will ask you to lie still on a table for the duration of the procedure (about 2 hours). You will be able to communicate with researchers all the time and you will have a panic button to use if you want to stop the procedure at any time.	You may feel slightly anxious inside the scanner due to a fear of small enclosed spaces (claustrophobia). Also, at times, you may hear very loud noises as the MRI machine is taking pictures of your body. You may be given headphones and may request ear plugs if you feel the noise is too loud. At any time, you may ask the technician to stop the exam if you are unable to complete the exam.
Physical Exam: Includes height, weight, vital signs (heart rate and blood pressure)	There are no physical risks associated with these procedures.
Concomitant Medications: You will be asked about your previous and current medications that you take.	There are no physical risks associated with these procedures.
Medical History Review: You will be asked about your medical and surgical history with attention to smoking, alcohol, and drug habits.	There are no physical risks associated with this procedure.
Urine Collection: Urine collection is a simple diagnostic procedure that measures the	No risks associated with this procedure.

components of urine. You will be asked to collect your urine in a special container so that it can be sent to a lab for analysis.	
Pregnancy Test: If you are a woman who is able to become pregnant, urine samples will also be used to do a pregnancy test	If your test is positive, you will be told and at that point you should discuss options available with your primary physician.
Demographic Information: You will be asked about your age, gender, race, ethnicity	There are no physical risks associated with these procedures.
Drug and alcohol screen: This is an assessment of your past or present use of drugs (such as, marijuana, cocaine, ecstasy). This will be completed by asking you to answer questions about your patterns of drug or alcohol use.	If you report a positive history of drug or alcohol use, this will be recorded as part of the study records. Study will follow all steps to protect the confidentiality of this information as outlined in the main consent form.
Saliva Collection: You will be asked to provide saliva samples which will be collected to measure elevated late evening cortisol.	There are no physical risks associated with this procedure.