

**STUDY TITLE: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 3 STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF PROGESTERONE IN PATIENTS WITH SEVERE TRAUMATIC BRAIN INJURY (PROTOCOL BHR -100-301)**

Principal Investigator: John Peter Gruen, M.D.

**EXPERIMENTAL SUBJECT'S BILL OF RIGHTS**

You have been asked to participate as a subject in a medical experiment. Before you decide whether you want to participate in the experimental procedure, you have a right to the following information:

**CALIFORNIA LAW REQUIRES THAT YOU MUST BE INFORMED ABOUT:**

1. The nature and purpose of the study.
2. The procedures in the study and any drug or device to be used.
3. Discomforts and risks reasonably to be expected from the study.
4. Benefits reasonably to be expected from the study.
5. Alternative procedures, drugs, or devices that might be helpful and their risks and benefits.
6. Availability of medical treatment should complications occur.
7. The opportunity to ask questions about the study or the procedure.
8. The ability to withdraw from the study at any time and discontinue participation without affecting your future care at this institution.
9. Be given a copy of the signed and dated written consent form for the study.
10. The opportunity to consent freely to the study without the use of coercion.

I have carefully read the information contained above and I understand fully my rights as a potential subject in this study.

Date: \_\_\_\_\_ Time: \_\_\_\_\_

Signature: \_\_\_\_\_  
(Research Participant)

Signature: \_\_\_\_\_  
(parent or legally authorized representative)

If signed by other than the research participant, indicate relationship: \_\_\_\_\_

Study ID: HS-10-00290 Valid From: 8/27/2010 To: 6/16/2011

## ADULT INFORMED CONSENT/YOUTH ASSENT/PARENTAL PERMISSION

**TITLE:** A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 3 STUDY TO INVESTIGATE THE EFFICACY AND SAFETY OF PROGESTERONE IN PATIENTS WITH SEVERE TRAUMATIC BRAIN INJURY (PROTOCOL # BHR-100-301)

**PRINCIPAL INVESTIGATOR:** JOHN PETER GRUEN, M.D.

**DEPARTMENT:** USC NEUROLOGICAL SURGERY

**SPONSOR:** BHR PHARMA, LLC

**24-HOUR TELEPHONE NUMBER:** 323 442-5720

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*If you are the parent or legally authorized representative providing consent on behalf of the participant, the word “you” in this consent refers to the person you are representing. If you are providing consent for a minor, your consent will remain effective and the minor will be asked to provide their assent to continue participation.*

*If you are the participant in this study, we would like to obtain your consent/assent to continue. If you would like to continue participation, you will be asked to sign the **Adult Consent/Youth Assent for Continued Research Participation** form attached to this consent. The study doctor or the study doctor’s staff will discuss with you which procedures and evaluations have already been done.*

We invite you to take part in a research study. Please take as much time as you need to read the consent form. You may also decide to discuss it with your family, friends, or your doctor. You may find some of the language difficult to understand. If so, please ask questions. If you decide to participate, you will be asked to sign this form.

### **WHY IS THIS STUDY BEING DONE?**

This study is about an experimental drug called BHR-100 and traumatic brain injury. Traumatic brain injury may lead to permanent or temporary impairment of mental, physical, and emotional functions, with a lack of or altered state of awareness. Traumatic brain injury is graded as mild, moderate, or severe based on standard medical tests.

BHR-100 is an experimental drug that has not been approved by the U.S. Food and Drug Administration (FDA). The primary component of BHR-100 is progesterone. Progesterone is a naturally produced hormone in men and women and an important agent affecting many functions in the central nervous system. It may play an important role in improving repair after a traumatic brain injury.

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We hope to learn about the safety and effectiveness of BHR-100 in its ability to limit damage to the brain and central nervous system when given after a traumatic brain injury.

You are invited as a possible participant because you have had a severe brain injury. About 10 participants will take part in this study at LAC+USC and about 1,180 participants worldwide.

### **WHAT IS INVOLVED IN THE STUDY?**

If you decide to take part, this is what will happen:

#### **Screening**

To make sure you are eligible to take part in the study the study doctor will ask about your medical history and the drugs you take. You will have a physical examination, including assessment of your level of consciousness and an x-ray of your brain called a CT scan. Your gender, age, and weight will be recorded. You will have standard blood tests (about 1 teaspoon) for routine blood chemistry, blood count, clotting ability and blood oxygen levels and urine tests (including a pregnancy test if you are a woman). An EKG (electrical activity of your heart) will be done. A small device that measures pressure may be placed inside the skull to measure how much brain swelling is happening due to the injury. These procedures are Standard of Care (SOC) which means they will be done regardless if you participate or do not participate in this study.

#### **Study Drug Administration Period (Days 1 – 5)/Post Infusion Evaluations (Days 6 and 15)/**

If the study doctor finds that you are eligible to take part in the study you will be randomly assigned to receive study drug, either BHR-100 or placebo. A placebo is a substance that looks like the active study drug but has no active ingredient. “Randomly assigned” means whether you receive BHR-100 or placebo will be decided by chance (like flipping a coin).

You will have an equal chance of receiving either BHR-100 or placebo. Both you and the study personnel will not know which study drug you will be receiving.

The study drug (BHR-100 or placebo) will be given by continuous infusion by vein (IV) for 5 days.

Your vital signs and level of awakesness will be recorded daily for as long as 15 days in total. In addition, standard medical treatment items will be recorded.

One blood sample, approximately 1 teaspoon, will be taken within the first 2 days of the study to measure the levels of progesterone in your blood. This blood collection is research related.

You will have a CT scan, urine test, and standard blood tests (about 1 teaspoon) for routine blood chemistry, blood count, clotting ability and blood oxygen levels 1 day after your last dose of study drug. An EKG (electrical activity of your heart) will be done.

You will have a urine test and standard blood tests (about 1 teaspoon) for routine blood chemistry, blood count, clotting ability and blood oxygen levels about 10 days after your last dose of study drug.

Your condition and any symptoms you develop during your participation in the study will be closely followed. Please tell the study doctor of any symptoms you may experience.

### **Follow Up Assessments (Month 1, 3, and 6)**

One month after you have completed the study drug, the study doctor or the study doctor's staff will follow up to see how you are doing in a clinic visit.

At three months and at six months after you have completed the study drug, the study doctor or the study doctor's staff will follow up to see how you are doing in a clinic visit. You will be asked to complete a questionnaire about your daily activities and how you are feeling so that the study doctor or the study doctor's staff will follow up to assess your day-to-day living activities and determine if you have returned to normal life (before your brain injury), or if you continue to struggle with the effects of your brain injury. Some of the questions may make you feel uneasy or embarrassed. You can choose to skip or stop answering any questions that make you uncomfortable.

Your participation in this study will last up to 6 months with a total of 7 study time points/visits (Screening, Day 1-5, Day 6, Day 15 and Months 1, 3 and 6.)

## **Information About Samples Collected as Part of this Research**

### **Sample collection for progesterone**

The blood sample collected for progesterone analysis will be labeled with the study number. Your sample will not have your personal information (such as your name and address) on it. Additionally, when your sample arrives at the laboratory, it will be given a second number. This second number will be used instead of the first number. The link between the first and second numbers will be unknown to the person doing the pharmacokinetic tests.

Your sample will be stored for up to five years after the end of the study and then will be destroyed by the laboratory. (The end of the study occurs when a final study report is completed.) Additional tests may be conducted during this time in case there are changes in the blood that are not known and may help better understand or develop treatments for traumatic brain injuries. The sponsor will not seek additional consent from you for the future use of your specimens for research purposes.

### **WHAT ABOUT PREGNANCY?**

We do not know whether this study drug might hurt your unborn baby. If you are pregnant, you cannot take part in this study. If you are a woman who could become pregnant, you must have a pregnancy test to make sure you are not pregnant. If you suspect that you are pregnant, you must notify the study doctor immediately.

If you are breastfeeding and do not want to stop, you may not take part in this study. The only way to take part in this study is to stop breastfeeding and not use your breast milk to feed your child until your doctor tells you it is safe.

### **WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?**

You will be monitored for any side effects. If you develop side effects, the study doctor will give you the care that you need.

Progesterone for the treatment of traumatic brain injury has been tested in three human studies.

In these studies, the only side effect attributed to progesterone was inflammation of the vein at the IV site in one participant, and this did not require medical treatment.

These three studies used various mixtures of progesterone. The mixture of progesterone in BHR-100 has not yet been studied in people with severe traumatic brain injury.

The following potential risks were previously identified as associated with prolonged (greater than 3 months) administration of progesterone (in women):

#### **Common Side Effects (> 5 in 100 participants):**

- Chest pain
- Viral infection
- Migraine (severe headache)

#### **Rare Side Effects (< 1 in 100 participants):**

- Heart attack
- Blood clots
- Stroke
- Liver function abnormalities
- Pneumonia
- Meningitis
- Allergic reaction
- Abnormal vision
- Fluid retention

There may be side effects that are not known at this time.

### **Blood Collection**

There may be pain, swelling, or bruising around the vein where your blood is collected. You may feel dizzy or you may faint. You may get an infection at the place on your body from which the blood is collected.

### **Placebo**

Some people in this study will receive placebo instead of BHR-100. Taking placebo is the same as not receiving any additional treatment for your traumatic brain injury (except for standard

medical care which you will continue to receive during the study). Please ask the study doctor or the study doctor's staff if you have any questions about placebo.

### **WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART IN THIS STUDY?**

You may not receive any direct benefit from taking part in this study. However, your participation in this study may help people in the future who suffer from a traumatic brain injury.

### **WHAT OTHER OPTIONS ARE THERE?**

You do not have to participate in this study to get medical treatment for your injury. Please discuss with the study doctor what other drugs and therapies may be available to treat your traumatic brain injury.

The effectiveness and side effects of other treatments may vary, depending on their suitability for an individual patient. You may ask the study doctor for more information about your condition and the possible benefits and risks of other available therapies, including no treatment at all.

An alternative would be to not take part in this study.

### **WILL YOUR INFORMATION BE KEPT PRIVATE?**

The investigator and the Institutional Review Board (IRB) will keep your records private as far as the law allows. The IRB is a research review board that is made up of professionals and community members who review and monitor research studies to protect the rights and welfare of research participants. Officials sent by the Food and Drug Administration (FDA), the sponsor, who is BHR Pharma, LLC, and sponsor's representatives may look at your research records and medical records. Your records will be kept confidential unless the law requires us to share these records. We may publish the information from this study in journals or present it at meetings. If we do, we will not use your name.

### **WHAT ARE THE COSTS?**

You and/or your health plan/insurance company will be responsible for the cost of any standard treatment and diagnostic procedures that you may receive for your illness. You and/or your health plan/insurance company/government program will be billed for the standard costs of treatment and diagnostic procedures in the same way as if you were not in a research study. You will also be responsible for any co-payments and deductibles that are standard for your health plan/insurance coverage. Some health plans will not pay these costs for people taking part in studies. Check with your health plan/insurance company/government program to find out what they will pay for. You and/or your health plan insurance company/government program will not be charged for the cost of any tests or procedures done solely for research purposes. If you have any questions about which tests or procedures will be billed to you and/or your health plan/insurance company, ask your doctor.

The study drug, blood sample collections for progesterone will be provided by the study sponsor free of charge while you are participating in this study.

**ARE THERE ANY PAYMENTS TO YOU FOR TAKING PART IN THE STUDY?**

You will not receive any payments for taking part in this study.

**Possible Commercial Products**

This study is part of the development of a new drug, which may be sold for profit. If the results of the studies are successful, the sponsor will not pay you anything for your participation in this study if BHR-100 is sold commercially. You will not profit financially from this product.

**WHAT HAPPENS IF YOU GET INJURED OR NEED EMERGENCY CARE?**

It is important that you tell your study doctor, **Dr. John Peter Gruen**, if you feel that you have been injured because of taking part in this study. You can tell the study doctor in person or call him at (323) 442-5720.

If you require medical treatment as a result of injury arising from your participation in this study, emergency medical care will be provided. The sponsor will pay for the cost of treatment for those injuries related to your participation in the study that are reasonable and necessary medical treatment of the injury that are not covered by your medical insurance, a government program or any other responsible third party. Such payment will be made to the extent such injury is not attributable to the normal progression of injury and to the extent that you followed all of the instructions provided by your doctor.

No other form of compensation will be provided for injuries resulting from your personal conduct or participation in activities outside of the scope of the study protocol. No financial compensation will be provided for such things as lost wages, disability or discomfort, losses claimed by spouses or family members, medical expenses due to treatment of any underlying or unrelated condition or any other expense arising from or claimed to be due to any research-related injury. However, by signing this form you have not given up any of your legal rights.

**WILL YOU RECEIVE NEW INFORMATION ABOUT THIS STUDY?**

During the study, we may learn new things about the risks or benefits of being in the study. If we do, we will share this information with you. You might change your mind about being in the study based on this information. If new information is provided to you, we will ask for your agreement to continue taking part in this study.

**CAN YOU BE REMOVED FROM THE STUDY?**

You may be removed from this study without your consent for any of the following reasons: you do not follow the investigator's instructions, at the discretion of the investigator or the sponsor, your disease gets worse, the sponsor closes the study, if you require a drug and/or treatment that is not allowed by the study, if you become pregnant, or if you do not later consent to any future changes that may be made in the study plan. If this happens, the investigator will discuss other options with you.

**WHAT ARE YOUR RIGHTS AS A PARTICIPANT, AND WHAT WILL HAPPEN IF YOU DECIDE NOT TO PARTICIPATE?**

Your participation in this study is voluntary. Your decision whether or not to take part will not affect your current or future care at this institution. You are not giving up any legal claims or rights. If you do decide to take part in this study, you are free to change your mind and stop being in the study at any time. If you leave the study early, you may be asked by the study doctor to have some of the end-of-study procedures done.

**WHOM DO YOU CALL IF YOU HAVE QUESTIONS OR CONCERNS?**

You may contact John Peter Gruen M.D. at (323) 442-5720 with any questions, concerns, or complaints about the research or your participation in this study or if you feel you have been hurt by taking part in this study. If you have questions, concerns, or complaints about the research and are unable to contact the research team, or if you want to talk to someone independent of the research team, please contact the Institutional Review Board (IRB) Office at 323-223-2340 between the hours of 8:00 AM and 4:00 PM. (Fax: 323-224-8389 or email at irb@usc.edu). If you have any questions about your rights as a research participant, please also contact the Institutional Review Board Office at the numbers above or write to the Institutional Review Board at the LAC+USC Medical Center, General Hospital Suite 4700, 1200 North State Street, Los Angeles, CA 90033.

You will get a copy of this consent form.

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**AGREEMENT:**

I have read (or someone has read to me) the information provided above. I have been given a chance to ask questions. All my questions were answered. I have decided to sign this form in order to take part in this study.

\_\_\_\_\_  
Name of Research Participant

\_\_\_\_\_  
Name of Witness

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date Signed

\_\_\_\_\_  
Name of Parent/Legally Authorized Representative

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date (& Time\*) of Signature

I have verbally translated this informed consent form to the research participant.

\_\_\_\_\_  
Name of Translator

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date of Signature

I have personally explained the research to the participant's legally authorized representative and answered all questions. I believe that he/she understands the information described and freely consents to participate.

\_\_\_\_\_  
Name of Investigator/Name of Person Obtaining Informed Consent

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date (& Time\*) of Signature

*\* If the study procedure is done on the same day of the signing the IC, the time and date are required. No study procedures should be done to the participant before his/her signing of the IC.*

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## ADULT CONSENT/YOUTH ASSENT FOR CONTINUED RESEARCH PARTICIPATION

You have been taking part in this research study: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study to Investigate the Efficacy and Safety of Progesterone in Patients with Severe Traumatic Brain Injury. Consent for your participation was initially obtained from your parent or legally authorized representative because you were unable to provide consent/assent at that time. We are now asking for you to consent/assent to continue being in the study. Your continued participation is entirely voluntary. If you decide not to continue in this study, it will not affect your relationship with your doctor or with **USC Neurological Surgery** and will not result in any penalty or loss of benefits to which you are otherwise entitled.

You will get a copy of this consent form.

### **AGREEMENT:**

I have read (or someone has read to me) the information provided above. I have been given a chance to ask questions. All my questions were answered. I have decided to sign this form in order to continue taking part in this study.

Name of Research Participant	Signature	Date Signed
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Name of Witness	Signature	Date Signed
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I have verbally translated this informed consent form to the research participant.

Name of Translator	Signature	Date of Signature
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I have personally explained the research to the research participant and answered all questions. I believe that he/she understands the information described and freely consents to participate.

Name of Investigator/Name of Person Obtaining Informed Consent	Signature	Date (& Time*) of Signature
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*\* If the study procedure is done on the same day of the signing the IC, the time and date are required. No study procedures should be done to the participant before his/her signing of the IC.*

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