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WALTER REED NATIONAL MILITARY MEDICAL CENTER
BETHESDA, MD

This consent form is valid only if it contains the IRB stamped date

Consent for Voluntary Participation in a Research Study Entitled: "Riluzole for PTSD: Efficacy of a Glutamatergic Modulator as Augmentation Treatment for Posttraumatic Stress Disorder".

Principal Investigator:

COL David Benedek, MD, MC
Professor/Deputy Chair, Psychiatry; Associate Director/Senior Scientist, Center for the Study of Traumatic Stress, USUHS
Service and Department: Psychiatry
USUHS, Building B
4301 Jones Bridge Road
Bethesda, MD 20184
Phone Number: (301) 295-9888
Mobile Number: (240) 204-0562
E-mail: david.benedek@usuhs.edu

Study site: x WRNMMC, FBCH, USUHS, WRAIR, x OTHER

List OTHER study sites: Syracuse VA Medical Center

"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."

1. INTRODUCTION OF THE STUDY

You are being asked to be in this research study because you are receiving treatment for posttraumatic stress disorder (PTSD) at WRNMMC, yet your symptoms have not improved. Your participation is voluntary. Refusal to participate will not result in any punishment or loss of benefits to which you are otherwise permitted. Please read the information below, and ask questions about anything you do not understand, before deciding whether to take part in the study.

2. PURPOSE OF THE STUDY

The purpose of the study is to learn and evaluate how using the drug riluzole (sold by the name Rilutek®) might improve the symptoms of PTSD in people who are not having improvement with their current medication. This is called an off-label study because although riluzole is approved to treat Lou Gehrig's disease, it is not presently approved for PTSD.

Other studies have shown that certain types of nerve cells in the brain, as well as specific areas of the brain are affected in people that experience PTSD. These affects may be caused by changes in the amount of glutamate that is normally found in the brain. Glutamate is a simple amino acid that acts as a messenger for nerve cells. Glutamate does this by binding to a nerve cell and telling it whether or not to activate. A medication like riluzole may lower the activity of glutamate in the brain, which may improve the symptoms of PTSD.

3. PROCEDURES TO BE FOLLOWED

If you agree to be in this study, you will be asked to take either riluzole or an identical looking but inactive placebo along with your current PTSD medication. You have a 50/50 chance of receiving riluzole or the placebo. Neither you, nor the study investigators, will know to which group (riluzole or placebo) you will be randomly assigned. The randomization process is like a coin toss done by computer. It will be conducted at the WRNMMC research pharmacy where you will go to receive your study drug (riluzole or placebo). You will take the study drug twice a day for 8 weeks.

At the Screening Visit, you and the study clinician will discuss the study and you will have a chance to ask any questions you might have about participating in the study. If you agree to participate you will be asked to sign this consent form. Then you will be evaluated by the study clinician for enrollment into the study. This medical evaluation will include your medical history, completion of six screening tests, surveys, and questionnaires, and a psychiatric and physical examination that includes blood tests for a profile of your blood, the functioning of your liver and thyroid, a pregnancy test for females and for HIV (Human Immunodeficiency Virus) and hepatitis. You will also give a sample of your urine for a urinalysis test (a common medical screening test) and a drug screen. This screening process is designed to ensure you are a good candidate for the study, have no major health complications and to provide information that can help the researchers determine whether or not the study drug is effective.

There is also an optional brain imaging portion of the study for which you can volunteer. This imaging is called a proton magnetic resonance spectroscopy, and it does not have any of the risks associated with X rays. It uses the same machine as an MRI, and if you are bothered by tight spaces (claustrophobia) you might not want to volunteer for this part of the study. There is one scan at the end of the screening visit, and the other after the trial. Each scan takes about an hour. Comparison of these scans may show if the study treatment improves parts of the brain that PTSD can adversely affect. If you want to volunteer for this we will ask you to sign another line at the end of the consent that is specific to the brain imaging portion of the study.

You will schedule the first Clinical Visit for two to four weeks after the Screening Visit. A number of tests will be conducted that day and it is when you will begin taking the study drug. During the two to four weeks after the Screening Visit you should continue taking your current PTSD medicine at the same dosage. You will be contacted by telephone after 1 week to confirm that no medication changes were made. Throughout the study you will continue taking the same amount of your original PTSD medicine while taking the study drug.

With your daily PTSD medicine dose stable and consistent, you will begin taking the study drug for PTSD. You will take two to four tablets twice a day of either riluzole or a placebo. You will begin by taking two tablets twice a day, but your dose may be increased if no improvement is noted during weekly

follow-up visits to the clinic. If on the higher dose, you experience any intolerable side effects or your liver functions exceed 3x the Upper Limit of Normal (ULN), your dose will be reduced to 100 mg/day. If your liver function test exceeds 3x ULN after a repeat test while on 100 mg/day, you will be removed from the study. If a participant's LFTs ever exceed 5x upper limit of normal, the study drug will be discontinued and the subject will be withdrawn from the study.

Remember, your chance of being assigned to either the riluzole or placebo group is equal. The placebo will look identical to riluzole, but it will not contain any amount of the active drug. You will not know whether you are taking the placebo or riluzole. Your clinician and the research staff will also not know whether you are taking the placebo or riluzole. This is called double blinding with a placebo and it is considered the best way to study the effect of drug. The research pharmacy will maintain a record of whether you are receiving study drug or placebo, so that the research team or external monitors could be informed in the event of an emergency (such as if you are admitted to the hospital and the treatment team needs to know what medications you are taking).

You will return for Clinical Visits weekly. You will meet with the study clinician to discuss any questions you have about the study. You will also give your medical history and complete several screening tests, surveys, and questionnaires as well as a psychiatric and physical examination. Finally, if you volunteered to participate in the brain imaging portion of the study, you will undergo a post-treatment scan between visits 8 and 9. At the end of your 10-week trial, you will be given the option of an additional 3-month, open-label treatment period with riluzole. If you choose to enter the additional open-label treatment period, an open-label letter will be provided to you to offer to your healthcare provider with guidance on appropriate monitoring.

4. ALTERNATIVES TO PARTICIPATION

Alternatives to participation may be available to you. You will need to consult with your primary care provider for other alternatives. Choosing not to participant in the study is an alternative to participation in the study. There may be other research studies involving experimental treatments that could help your condition.

5. AMOUNT OF TIME FOR YOU TO COMPLETE THE STUDY

You will be part of this study for 10 weeks and at the end of study participation you will be given the option of receiving riluzole for an additional 3-month period of treatment. This option is available to everyone whether or not you believe you received the placebo or the study drug during your 10 weeks of study treatment.

During the 10 weeks of the study, you will be asked to visit the clinic 9 times. In the first two weeks, you will visit the clinic for your first visit, the Screening Visit, which will take 4 hours, and you will have a follow-up telephone interview, which lasts approximately 10 minutes. In the remaining 8 weeks, you will visit the clinic weekly, which may take between 2 to 4 hours, each.

The time commitment for the participants who volunteer to complete the imaging part of the study at the Screening Visit and the last visit, is estimated to be 60 to 90 minutes for each scan.

6. NUMBER OF PEOPLE THAT WILL TAKE PART IN THIS STUDY

This study is called a multi-site study because participants from two hospitals will be in the study. There will be up to 104 people taking part in this study at WRNMMC and up to 54 people taking part in this study at the Syracuse VA Medical Center. A total of 158 people will be in the study from the two hospitals involved.

7. POSSIBLE RISKS OR DISCOMFORTS FROM BEING IN THIS STUDY

The possible risks and discomforts from being in this research study include:

Screening and Evaluation: The risks and discomforts of the screening and baseline evaluations are minimal. No discomfort is expected to be associated with the physical examination or the clinical interview. Venipuncture, drawing a small amount of blood at each visit, may be commonly associated with the momentary discomfort of the needle stick, as well as a small, but rare risk of a bruise forming. You will be exposed to the discomfort of asking personal questions that you may find distressing.
While uncommon, if you experience significant psychological stress while answering study questionnaires, the study clinician will evaluate your immediate needs and provide you with appropriate mental health referrals and resources. There are no social, legal, or financial risks or discomforts expected with your participation in this study.

Risks Due to Taking Riluzole: The risks and discomforts of taking riluzole are rare. Earlier studies on individuals taking riluzole found most people having minimal problems even when taking multiple, different medications at the same time.

Those people that did have trouble with riluzole commonly experienced nausea and overall weakness and fatigue or tiredness. While rare, some individuals had higher laboratory test results for the functioning of their liver (their liver enzyme levels had increased), but these levels returned to normal once they stopped taking riluzole. We will be testing the functioning of your liver each week while you are taking riluzole to watch for this condition and you will stop taking riluzole if this happens to you.
You should know that alcohol use is discouraged while taking riluzole because the combination of the two can affect the functioning of your liver (your liver enzyme levels could increase). If you have an abnormal (high) liver function test result while taking riluzole, and it's possible the result occurred due to your alcohol consumption while taking riluzole, be sure to inform the clinician that your test result is not due exclusively to your taking riluzole. The clinician will discuss with you confidentially your options.

Rarely, a condition called interstitial lung disease (scarring of the lung tissue) has occurred in some patients who have taken riluzole. If you develop a dry cough with shortness of breath or difficulty breathing, you need to see a doctor and get a chest x-ray and you may have to stop taking riluzole immediately. If this happens, in most cases, the symptoms end after stopping the drug and receiving treatment for the symptoms.

While rare, some of the people who took the highest dose of riluzole per day in past studies also had dizziness, diarrhea, anorexia, tremor, exfoliative dermatitis or had unknown skin sensations like burning, prickling, itching, tingling. Another rare possibility is pancreatitis, or inflammation of the pancreas. If

untreated pancreatitis may result in severe abdominal pain or even death, however these reported cases were resolved by withdrawing Riluzole treatment. Very rarely (3 reported cases out of 5,000 patients) there have been reports of neutropenia, a condition in which certain white blood cell counts are decreased and may result in a weakened immune system without treatment. You will meet weekly with the study clinician, and the two of you will discuss any symptoms or feelings or side effects you are having while taking riluzole. If you experience these rarer symptoms, the study clinician will discuss with you the possible changes that can be made in your study participation.

Risks Associated with Magnetic Resonance Spectroscopy: The magnetic resonance imaging scan that some participants in the study will volunteer to do for brain imaging is not associated with any known harmful effects. However, there are risks for people who have any metallic implants in their body. For this reason, you will be asked whether you have any metallic implants at the time of recruitment and just prior to the imaging scan. Also, since the imaging study requires that a person lie relatively still in relatively narrow cylindrical tube, some persons may experience uneasiness or discomfort from being in such a space. If you experience these feelings and they become excessive, you can request that the study be stopped.

General: By agreeing to participate in this study, you are agreeing to receive an unproven treatment (a 50% chance because you could receive the placebo) for your PTSD symptoms, which may not decrease, lessen or otherwise improve these symptoms. Alternatively, you may be able to receive this treatment from your physician. Riluzole is available for prescription by a physician. However, it does not have FDA-approval for the treatment of PTSD. Your participation in this study could help physicians know whether riluzole is effective in treating PTSD symptoms.

8. POSSIBLE BENEFITS FROM BEING IN THIS STUDY

You may or may not benefit from taking part in this study, but the information we learn may help us learn about the active study drug for the treatment of PTSD that might improve the symptoms of this condition in people who are not having improvement under their current medication.

9. CONFIDENTIALITY/PRIVACY OF YOUR IDENTITY AND YOUR RESEARCH RECORDS

The principal investigator will keep your research records secured at all times. These records will be stored in locked cabinetry in a locked room accessible only by the research study team. All electronic research information and data will be maintained under password protection and data encryption. These records may be looked at by staff from the Walter Reed (WRNMMC) Department of Research Programs, the Walter Reed (WRNMMC) Institutional Review Board (IRB), the DoD Higher Level Review, the Veterans Health Administration Research and Development Institutional Review Board (IRB), and other government agencies as part of their duties. These duties include making sure that the research participants are protected. Confidentiality of your records will beprotected to the extent possible under existing regulations and laws but cannot be guaranteed.

Complete confidentiality cannot be promised, particularly for military personnel, because information bearing on your health may be required to be reported to appropriate medical or command authorities. Your research records may be disclosed outside of WRNMMC, but in this case, you will be identified only

by a unique code number. Information about the code will be kept in a secure location and access limited to authorized research study personnel.

By signing this consent document, you give your permission for information gained from your participation in this study to be published in medical literature, discussed for education purposes, and used generally to further medical science. You will not be personally identified; all information will be presented as anonymous data. So, your name will not appear in any published paper or presentation related to this study.

This research study meets the confidentiality requirements of the Health Insurance Portability and Accountability Act (HIPAA).

10.CONDITIONS UNDER WHICH YOUR PARTICIPATION IN THIS STUDY MAY BE STOPPED WITHOUT YOUR CONSENT

Your taking part in this study may be stopped without your consent if remaining in the study might be dangerous or harmful to you. Your taking part in this study may also be stopped without your consent if the military mission requires it, or if you lose your right to receive medical care at a military hospital. Lastly, your taking part in this study may be stopped without your consent if you do not take the study drug or your preexisting PTSD medication. If you begin evidence based psychotherapy (such as CPT or prolonged exposure therapy) or if any of the medications you take for PTSD or other psychiatric conditions are changed after you begin the study, you may be withdrawn from the study.

11. ELIGIBILITY AND PAYMENT FOR BEING IN THIS STUDY

You will be compensated for the time you spend completing the study assessments. If you are active-duty military, you must be off-duty during participation to receive compensation. This compensation will be a gift card given to you by a study member at the end of each visit. Compensation will be as follows:

Screening:	$75 (5 hours)
Visit 1:	$60 (4 hours)
Visit 2:	$30 (2 hours)
Visit 3:	$30 (2 hours)
Visit 4:	$30 (2 hours)
Visit 5:	$60 (4 hours)
Visit 6:	$30 (2 hours)
Visit 7:	$30 (2 hours)
Visit 8:	$30 (2 hours)
Visit 9:	$60 (4 hours) Bonus

for attending all sessions: $80

Bonus for completing both the pre- and post- ^{1}H MRS imaging scans: $75 (5 hours)

Total possible compensation: $590

Compensation will be prorated as a percentage of the full payment for incomplete research sessions.

12. COMPENSATION IF INJURED AND LIMITS TO MEDICAL CARE

You will not receive any compensation (payment) if you are injured as a direct result of being in this study. You should understand that this is not a waiver or release of your legal rights. You should discuss this issue thoroughly with the principal investigator before you enroll in this study.

Should you be injured as a result of your participation in this study, you will be given medical care for that injury at no cost to you.

Medical care is limited to the care normally allowed for Department of Defense health care beneficiaries (patients eligible for care at military hospitals and clinics). Necessary medical care does not include in-home care or nursing home care.

If at any time you believe you have suffered an injury or illness as a result of participating in this research project, you should contact the Department of Research Programs at Walter Reed National Military Medical Center at 301-295-8239.

13. COSTS THAT MAY RESULT FROM TAKING PART IN THIS STUDY

There is no charge to you for taking part in this study.

14. IF YOU DECIDE TO STOP TAKING PART IN THIS STUDY AND THE INSTRUCTIONS FOR STOPPING EARLY

You have the right to withdraw from this study at any time. If you decide to stop taking part in this study, you should tell the principal investigator as soon as possible; by leaving this study at any time, you in no way risk losing your right to medical care. Some period of observation by the investigators may be recommended for you in order for you to safely stop taking part in this study because of the study drug.

15. STEPS TAKEN BEFORE AND DURING THIS STUDY TO PROTECT YOU

Riluzole has been classified by the FDA as a Class C drug, which means animal testing has shown an adverse effect on the fetus but there is no available data from human studies. If you are pregnant or breast feeding, you cannot take part in this study. Females of childbearing age must take a urine or blood pregnancy test before starting this study. If this test is positive, you cannot take part in this study. If you are a female, you should avoid becoming pregnant for at least one month after last receiving the study drug. Female participants will also be required to take a pregnancy test upon completion of the study. Male participants should understand that studies have not shown what effect riluzole can have on human sperm. Since it is not known if riluzole can adversely affect human sperm, there could be a risk to a child conceived while a man is taking riluzole. If you are a male, you should avoid trying to conceive for at least once month after last receiving the study drug.

16. YOUR RIGHTS IF YOU TAKE PART IN THIS STUDY

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care.

17. AUTHORIZATION FOR RESEARCH USE OF PROTECTED HEALTH INFORMATION

The Federal Health Insurance Portability and Accountability Act (**HIPAA**) includes a Privacy Rule that gives special safeguards to Protected Health Information (**PHI**) that is identifiable, in other words, can be directly linked to you (for example, by your name, Social Security Number, birth date, etc.). We are required to advise you how your PHI will be used. This authorization is effective until this study is closed.

(1) What information will be collected?

For this research study, we will collect information about your overall health status, any side effects that you are experiencing while taking the study drug, and how the study drug is affecting your PTSD symptoms. The PHI we will collect from you includes your name, address, phone number, date of birth, and email address and social security number.

(2) Who may use your PHI within the Military Healthcare System?

The members of the research team will have access to your health information in order to find out if you qualify to participate in this study, to administer the study drug, to monitor your progress, and to analyze the research data. Additionally, your PHI may be made available to research oversight groups such as the WRNMMC Department of Research programs and the WRNMMC Institutional Review Board.

(3) What persons outside of the Military Healthcare System who are under the HIPAA requirements will receive your PHI?

The Principal Investigator or designee will send your PHI to the company that makes riluzole only under extreme circumstances, such as a medical emergency or court order. If you experience a complication, we may need to send a copy of your medical record (with your name and other personal identifying information blacked out) to the company that makes riluzole and the Food and Drug Administration. Finally, your PHI may be made available to research oversight groups such as the Syracuse VA Medical Center, and the Veterans Health Administration Research and Development Institutional Review Board (IRB).

(4) What is the purpose for using or disclosing your PHI?

a. The members of the research team need to use your PHI in order to analyze the information to

find out whether the study drug we are testing is effective and to monitor your safety.

(5) How long will the researchers keep your PHI?

The research team will keep the research data for a minimum of seven (7) years after the end of the study. At that time, all the information will be destroyed. This consent form and HIPAA authorization will be maintained for a minimum of six (6) years after the study is completed.

(6) Can you review your own research information?

a. You will not be able to look at your research information until the study has ended.

(7) Can you cancel this Authorization?

Yes. If you cancel this Authorization, however, you will no longer be included in the research study. The information we collected from you can be destroyed at your request. If you want to cancel your Authorization, please contact the Principal Investigator in writing at the following:.

David M. Benedek, MD
Uniformed Services University of the Health Sciences Department of Psychiatry
4301 Jones Bridge Road Bethesda,
Maryland 20814-4799

(8) What will happen if you decide not to grant this Authorization?

If you decide not to grant this Authorization, you will not be able to participate in this research study. Refusal to grant this Authorization will not result in any loss of medical benefits to which you are otherwise entitled.

(9) Can your PHI be disclosed to parties not included in this Authorization who are not under the HIPAA requirements?

There is a potential that your research information will be shared with another party not listed in this Authorization in order to meet legal or regulatory requirements. Examples of persons who may access your PHI include representatives of the DoD Higher Level Review, the Food and Drug Administration, the Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP), and the DHHS Office for Civil Rights. This disclosure is unlikely to occur, but in that case, your health information would no longer be protected by the HIPAA Privacy Rule.

(10) Who should you contact if you have any complaints?

If you believe your privacy rights have been violated, you may file a written complaint with the WRNMMC Privacy Officer, located at 8901 Wisconsin Ave, Bethesda, MD 20889, Telephone: 301-

319-4775,

Your signature at the end of this document acknowledges that you authorize WRNMMC personnel to use and disclose your Protected Health Information (PHI) collected about you for research purposes as described above.

18. CONTACTS FOR QUESTIONS ABOUT THE STUDY

If you have questions about the study, or if you think you have a study-related injury you should contact **David Benedek, MD** at **301-295-9888 or after hours at 240-204-0562**. For questions about your rights as a research participant, contact the Human Protections Administrator, Department of Research Programs in Building 17 at (301-295-8273) or Staff Judge Advocate Office at 301-295-2215.

If you believe you are experiencing a medical emergency, please contact 911 or your local emergency medical service.

A signed copy of this consent form will be provided to you.

SIGNATURE OF RESEARCH PARTICIPANT

You have read (or someone has read to you) the information in this consent form. You have been given a chance to ask questions and all of your questions have been answered to your satisfaction.

BY SIGNING THIS CONSENT FORM, YOU FREELY AGREE TO TAKE PART IN THE RESEARCH IT DESCRIBES.

Participant's Signature	Date	Time

Participant's Printed Name

If you wish to volunteer for the brain imaging part of the study please sign below.

"I wish to volunteer to participate in the proton MRS imaging portion of the study."

Participant's Signature	Date	Time

Participant's Printed Name

SIGNATURE OFRESEARCH TEAM MEMBER OBTAINING CONSENT

You have explained the research to the participant and answered all of his/her questions. You believe that the volunteer subject understands the information described in this document and freely consents to participate.

Signature of Person Obtaining Consent Date (must be the same as the participant's) Time

Printed Name of Person Obtaining Consent