

Emory University School of Medicine
Consent to be a Research Subject

Title: Clinical trial of ceftriaxone in subjects with ALS-Stage 3

Principal Investigator: Jonathan D. Glass, M.D.

Sponsor's Name: The National Institutes of Health (NIH)/National Institute of Neurological Disorders and Stroke (NINDS) through Massachusetts General Hospital.

Introduction:

You are being asked to be in a medical research study. This form is designed to tell you everything you need to think about before you decide to consent (agree) to be in the study or not to be in the study. **It is entirely your choice. If you decide to take part, you can change your mind later on and withdraw from the research study.** The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.

- Please carefully read this form or have it read to you
- Please listen to the study doctor or study staff explain the study to you
- Please ask questions about anything that is not clear
- Feel free to take home an unsigned copy of this form and take your time to think about it and talk it over with family or friends

If you agree to join this research study, you will receive a copy of this consent form with your signature and the date, to keep. Do not sign this consent form unless you have had a chance to ask questions and get answers that make sense to you. Nothing in this form can make you give up any legal rights. By signing this form you will not give up any legal rights.

Purpose: You are being asked to volunteer for a research study to test the safety and effect of ceftriaxone treatment in Amyotrophic Lateral Sclerosis (ALS). You have been invited because you have been diagnosed with ALS.

It is known that the nerve cells called “motor neurons” die in the brains and spinal cords of people with ALS. However, the cause of the cell death is unknown. Researchers think that increased levels of a chemical called “glutamate” may be related to the cell death. For this reason, researchers want to study drugs that decrease glutamate levels near nerves. We are interested in studying ceftriaxone because the drug may increase the level of a protein that decreases glutamate levels near nerves. Studies of ceftriaxone in the laboratory suggest that it may protect motor neurons from injury.

Ceftriaxone is approved by the U.S. Food and Drug Administration (FDA) for the treatment of bacterial infections but not for the treatment of ALS. Ceftriaxone is also not approved for daily use for longer than 6 weeks. The use of ceftriaxone for the treatment of ALS is investigational. This means that ceftriaxone is being tested in research

studies as a possible treatment for ALS. Ceftriaxone has not been given to people over a long period of time, such as months or years. The long-term use of ceftriaxone is also being studied.

The only drug that has shown positive effects on the course of ALS is Riluzole, a drug that slows the release of glutamate. Riluzole is approved by the FDA for treatment of ALS. Two studies have shown that subjects with ALS who took Riluzole lived about 3 months longer than expected. Subjects who take part in this study will be able to take Riluzole. However, they must be on the same dose of Riluzole for at least 30 days before they can start the study drug.

Study Information:

Sixty subjects have already completed stages 1 & 2. This consent form is for stage 3.

Stages 1 & 2 consisted of a double-blind study where the subjects were selected by chance (like tossing a coin) to be in one of three groups. Before beginning stage 3, the information from stages 1 and 2 has been looked at by a safety committee (Data and Safety Monitoring Board, appointed by the National Institutes of Health's neurology division, called NINDS) and the committee responsible for guiding the progress of the trial (the Steering Committee, made up of doctors who are in the fields involved in the study), and a decision has been made that the trial is able to move forward, based on safety data. These groups have also decided what dose of ceftriaxone is best for stage 3 of the trial.

All 60 subjects who participated in stages 1 & 2 of the study will continue into stage 3. An additional 540 subjects will participate in the study in stage 3. If you choose to participate, you will be one of these 540 subjects. At the end of the study, a total of 600 subjects will have participated in the study at up to 70 sites across the U.S. and Canada. We plan to screen a total of about 30 people with ALS for the study at Emory to find 15 who meet the study requirements.

The study will end after the last subject enrolled has taken the study drug for 52 weeks (one year). The length of time it takes you to complete the study will depend upon when you started the study. The shortest time to complete the study will be 52 weeks. The longest time to complete the study will be 5 years. Over the 5 years, subjects will be asked to make up to 70 visits to Emory.

You will be given the study drug (ceftriaxone or placebo) twice a day through a central venous catheter placed in your neck. A central venous catheter is used for long-term intravenous (IV) access. Central venous catheters are used when patients need many weeks or a few months of treatment with antibiotics, chemotherapy, or nutritional support. The central venous catheter will be used only to give you the study drug and cannot be used for other purposes during the study. The catheter may have to be replaced during the study. The likelihood of the catheter needing replacement is unknown and will depend on side effects due to the catheter.

This study uses a placebo. The placebo looks like the study drug, but contains no ceftriaxone. Placebos are used to tell whether the effects seen are really from the study drug. The placebo used for this study is a low dose of pediatric multi-vitamin.

During stage 3 (the stage in which you are entering the trial), research subjects will be assigned randomly (by chance, like a coin toss) to one of two study groups:

One group (2/3, or 67%, of subjects) will receive 4 grams per day of ceftriaxone

One group (1/3, or 33%, of subjects) will receive Placebo

Neither you nor the researchers can choose your study group assignment. This is a “double-blind” study, which means that neither you nor the members of the research team will know which study group you are assigned to, but we can find out in an emergency. You have a 2 out of 3 chance of getting ceftriaxone and a 1 out of 3 chance of getting placebo.

If you are selected to receive ceftriaxone as your study drug, you will also receive a medication (ursodiol) that you will take orally two times a day. This medication is being used to lower the risk of developing gallbladder problems, which is an expected side effect of ceftriaxone. If you are selected to receive placebo study drug, you will receive a placebo medication (instead of ursodiol) that you will take orally two times a day. This placebo medication will look like ursodiol, but will contain no active drug.

You cannot take part in this study if you:

- Are less than 18 years old
- Are pregnant
- Are allergic to Penicillin or other cephalosporin antibiotics, such as Ancef, Keflex, Ceclor, Ceftin, Lorabid, Suprax, and Fortaz
- Have a history of another neurological disorder (other than ALS)

Procedures:

The first visit for the study is the Screening Visit. The purpose of this visit is to find out if you meet all of the requirements to participate in the study. The second visit is the Central Venous Catheter Placement Visit. Upon successful placement of the Central Venous Catheter the subject will be “randomized” into the study and the Baseline Visit will be performed.

Screening Visit

The Screening Visit will take about **4-6 hours**. During this visit, the following procedures will be done to see if you meet the study requirements and are eligible to take part in the study:

- Obtain written informed consent
- Assessment of inclusion and exclusion criteria

- Medical history and complete physical exam
- Vital signs (blood pressure, heart and respiratory rates, temperature) and weight
- Review of current medications
- Blood drawn for routine laboratory tests (about 2 teaspoons)
- For women able to have children, blood drawn for pregnancy test (1 teaspoon)
- Urine collected for routine tests
- Vital capacity test (VC) to check breathing capacity
- Abdominal ultrasound to check for gallbladder disease
- ALS Functional Rating Scale, Revised – ALSFRS-R (a questionnaire about ability to function in certain daily activities)
- Subject and caregiver quality of life questionnaires (ALSSQOL)
- Strength testing of arm and leg muscles
- Teaching of drug administration and care of the Hickman catheter will take place over **2-6 hours** and will begin on this day and be continued on another day.

Descriptions of Procedures:

- Vital Capacity (VC) Testing: The VC measures the maximum amount of air you can exhale following a deep breath. For this test, you will be asked to hold a mouthpiece in your mouth, breathe in deeply, and breathe out as long and hard as you can.
- Abdominal Ultrasound: An ultrasound is a test that uses sound waves to get a picture of your insides, in this case your gallbladder. You will lie on a table and the doctor or nurse will use a transducer (hand-held device) and gel that is applied to your skin, running the transducer over the skin of your abdomen. Ultrasound waves cause no sensation and the only thing you will feel is the pressure of the transducer on your skin.
- ALS Functional Rating Scale – Revised (ALSFRS-R) Questionnaire: this questionnaire consists of 12 questions about your ability to function in certain daily activities. Although we hope you will answer all questions, you can skip any questions that you do not want to answer. This questionnaire will take about 5-10 minutes to answer.
- ALS-Specific Quality of Life (ALSSQOL) Questionnaire and Caregiver Burden-Inventory: You and your caregiver will be asked to fill out questionnaires that pertain to your quality of life. One (that you will fill out) is an ALS-specific Quality of Life Scale, and one (that your caregiver will fill out) is called the Caregiver Burden Inventory. You can skip any questions that you do not want to answer. These questionnaires will take about 15-20 minutes to answer.
- Strength testing: You will have muscle strength testing performed on your upper and lower limbs. For this procedure, the coordinator will hold a small device (called a hand-held dynamometer) in his or her hand and will push against your arms and legs while you try to hold against this pushing. This testing will take approximately 15 minutes. This should not hurt, but may be slightly uncomfortable due to pressure and may make your muscles tired.

The investigator (doctor) or research nurse will call you in about one week to tell you if you are eligible to take part in this study. If you are eligible, you will be asked to return within

26 days of the screening visit to have a central venous catheter placed. The study drug (ceftriaxone or placebo) will be given through this catheter.

Central Venous Catheter Placement Visit

Placement of the central venous catheter will take place in the Interventional Radiology Department at Emory University Hospital. The procedure will be explained to you in detail by the radiologist or nurse practitioner that will do the procedure. You may be asked by the radiologist to sign a separate consent form to show that you agree to have the procedure done. This visit will take about **6 hours**. Except in rare cases, this visit will not require an overnight stay in the hospital. Before the central venous catheter is placed we will check your vital signs and review your current medications. Placement of a central venous catheter involves the following:

The radiologist uses ultrasound to see if the vein at the base of your neck is suitable (easily identified). Before the procedure, an intravenous (IV) catheter is placed in a vein in your arm to give IV antibiotics to prevent infection. An IV catheter is a very thin flexible plastic tube that is inserted into a vein using a needle. We may give you medication before the procedure to help you relax. The area is cleaned thoroughly with an antiseptic solution and sterile cloths are placed over the area to lower the risk of infection. A local anesthetic is injected to numb the area. Once the area is numb, the radiologist makes a small cut in the skin. A needle is then inserted through the cut in the skin and placed in the vein at the base of the neck, known as the jugular vein. The radiologist creates a tunnel under the skin from the upper chest to the neck incision. The catheter is passed through the tunnel and into the jugular vein. The tip of the catheter is placed in the main vein of the chest. The radiologist uses ultrasound to guide and check the placement of the catheter. In some cases, the radiologist may also use a type of X-ray, called "fluoroscopy" to guide the catheter placement as well. One or two stitches are used to close the small cut at the base of the neck and a stitch is also used around the catheter on the outside to hold it in place. The catheter will exit the skin in the upper chest, and will look something like an IV. The place where the catheter exits the skin is called the "exit site." A Dacron-fiber cuff is placed below the skin to hold the catheter in place and to prevent infection. Over time, body fluids cause the cuff to expand and tissue forms in and around it to hold it in place. Following the placement procedure, an X-ray is done to check the catheter placement. You will stay in the Interventional Radiology suite for about **2 hours** to make sure that you are doing well and that there are no problems.

The catheter extends outside the chest by about 12 inches. While this may be accepted easily for some, it may cause negative feelings related to body image or sexuality issues for others. Once the wound heals, it is safe to do most normal activities of daily living. Sports activity is permitted except for contact sports where there is a risk of the catheter being pulled out. Showering is permitted, once the incision is healed and this is approved by the study nurse or doctor. The dressing site should be covered with plastic and securely fastened around the edges with tape to prevent the dressing from getting wet. If the dressing does get wet, it should be changed. The catheter should not be placed underwater (taking a tub bath, hot tub, etc). Swimming is also not permitted.

During the study, if you need to have the catheter removed temporarily, you may have to stop taking the study drug until the catheter is replaced. In some situations, you may be given the option of receiving the study drug through a different kind of intravenous (IV) line, called a peripheral line, until the catheter can be replaced. If this is necessary, your study doctor will discuss the options with you.

Pre-Randomization Central Venous Catheter Check

After your catheter is placed, and before you have your Baseline visit (when you will begin taking the study drug), a member of the site staff will check the catheter and the exit site. This “check” is to make sure that the catheter is functioning properly and that there are no signs of infection. The visit may be at the site, or may be at your home. The visit will occur only if the Catheter Placement and Baseline Visits do not occur on the same day. If there are any problems with the catheter (if it is not working or if the medical person who checks it feels that it is infected), you will not be able to start study drug until the problem is resolved.

Baseline Visit (Day 0)

The Baseline Visit will take place no more than 28 days after the screening visit. This visit may take place on the same day as the central venous catheter placement visit, or on a different day. The baseline visit will take about **2 hours**. During this visit, the following procedures will be done:

- Review of changes in your condition
- Review of current medications
- Vital signs and weight
- Check of central venous catheter site
- Distribution of study drug, and ursodiol or placebo medication

At this visit you will begin taking the study drug (ceftriaxone or placebo). You will take the study drug twice a day. The study drug is provided in pre-filled syringes (small containers that hold the drug and attach to the tubing). The pre-filled syringes must be kept in the freezer until you are ready to use them. The study drug must be thawed before use and cannot be re-frozen after it has been thawed. Giving you the study drug includes inserting the syringe into the pump, preparing the tubing, connecting the tubing to the end of the catheter and setting the pump. Before you begin taking the study drug, we will teach you and your caregiver how to give the drug, and you will have time to practice and ask questions. We will also give you and your spouse/caregiver detailed written instructions on how to store, thaw, and give the study drug when we give you your first batch of pre-filled syringes. You will be asked to bring any unused study drug and the empty syringes with you at each study visit.

For the first two weeks, a nurse that specializes in home infusion catheters (which are like central venous catheters) will be available to come to your home. The home infusion nurse will look at your catheter and check for signs of infection. In addition, the nurse will make

sure you know how to take care of the catheter, how to take the study drug and how to change the dressing. The nurse may continue to visit you in the home if Dr. Glass thinks that it is medically necessary.

At this visit you will also receive a bottle of ursodiol or placebo medication. You will take this medication orally twice a day. You will be asked to bring any unused medication with you at each study visit.

Following the Baseline Visit, you will return to Emory each week for the next two weeks, and then once every 4 weeks. These three visits: Central Venous Catheter Placement visit, Pre –Randomization Central Venous Catheter Check, and the baseline visit are usually conducted on the same day and will take about **8 hours**.

Week 1 and Week 2 Visits

These study visits will each take about **2 hours**. During these visits, the following procedures will be done:

- Review of side effects or changes in your condition
- Review of current medications
- Vital signs
- Check of central venous catheter site
- Blood drawn for routine laboratory tests (just over 2 teaspoons)
- Urine collected for routine tests of kidney function
- Review of Catheter Care and study drug administration procedures with you and your caregiver as needed

Week 4 Visit

You will be given a 4 week supply of study drug (ceftriaxone or placebo) along with ursodiol or matching placebo medication at this visit. You will bring your filled-out study diary, unused medication and study drug syringes (empty and un-used) to this visit. During this visit the following procedures and tests will be performed:

- Review of side effects or changes in your condition
- Review of current medications
- Vital signs and weight
- Check of central venous catheter site
- Blood drawn for routine laboratory tests (just over 2 teaspoons)
- Urine collected for routine tests of kidney function
- Vital capacity test (VC) to check breathing capacity
- ALS Functional Rating Scale, Revised (ALSFRS-R)
- ALS Specific Quality of Life Questionnaire (ALSSQOL)
- Strength testing of arm and leg muscles
- An abdominal ultrasound to check for gallbladder disease*

* The abdominal ultrasound procedure will be performed at Week 4, Week 8, and Week 20 visits. If an abdominal ultrasound shows evidence of gall bladder problems, an abdominal ultrasound will be repeated at regular intervals until this condition resolves.

Week 8 Visit

You will be given a 4 week supply of study drug (ceftriaxone or placebo) along with ursodiol or matching placebo medication at this visit. You will bring your filled-out study diary, unused medication and study drug syringes (empty and un-used) to this visit. During this visit the following procedures and tests will be performed:

- Review of side effects or changes in your condition
- Review of current medications
- Vital signs
- Check of central venous catheter site
- Blood drawn for routine laboratory tests (just over 2 teaspoons)
- Urine collected for routine tests of kidney function
- An abdominal ultrasound to check for gallbladder disease*

*The abdominal ultrasound will be performed at Week 4, Week 8, and Week 20, and then as needed throughout the study. If an abdominal ultrasound is performed and shows evidence of gall bladder problems, additional ultrasounds may be performed at regular intervals until the problem resolves.

These same procedures will be performed at the Week 20 Visit

Week 12 Visit

You will be given a 4 week supply of study drug (ceftriaxone or placebo) along with ursodiol or matching placebo medication at this visit. You will bring your filled-out study diary, unused medication and study drug syringes (empty and un-used) to this visit. During this visit the following procedures and tests will be performed:

- Review of side effects or changes in your condition
- Review of current medications
- Vital signs
- Check of central venous catheter site
- Blood drawn for routine laboratory tests (just over 2 teaspoons)
- Urine collected for routine tests of kidney function

These same procedures will be performed at the Week 28, 36, 44, 52**, 60, 68, 76, 84, 92, 100, 108, 116, 124, 132, 140, 148 and 156 Visits

**At the Week 52 Visit, a Complete Physical Examination will be performed in addition to the tests listed above.

Week 16 Visit

You will be given a 4 week supply of study drug (ceftriaxone or placebo) along with ursodiol or matching placebo medication at this visit. You will bring your filled-out study diary, unused medication and study drug syringes (empty and un-used) to this visit. During this visit the following procedures and tests will be performed:

- Review of side effects or changes in your condition
- Review of current medications
- Vital signs and weight
- Check of central venous catheter site
- Blood drawn for routine laboratory tests (just over 2 teaspoons)
- Urine collected for routine tests of kidney function
- Complete physical exam
- Additional blood drawn (2 teaspoons) to measure ceftriaxone levels
- Vital capacity test (VC) to check breathing capacity
- ALS Functional Rating Scale, Revised (ALSFRS-R)
- ALS Specific Quality of Life Questionnaire (ALSSQOL)
- Strength testing of arm and leg muscles

Week 24 Visit

You will be given a 4 week supply of study drug (ceftriaxone or placebo) along with ursodiol or matching placebo medication at this visit. You will bring your filled-out study diary, unused medication and study drug syringes (empty and un-used) to this visit. During this visit the following procedures and tests will be performed:

- Review of side effects or changes in your condition
- Review of current medications
- Vital signs
- Check of central venous catheter site
- Blood drawn for routine laboratory tests (just over 2 teaspoons)
- Urine collected for routine tests of kidney function
- ALS Functional Rating Scale, Revised (ALSFRS-R)

These same procedures will be performed every sixteen weeks at Week 40, 56, 72, 88, 104, 120, 136 and 152 Visits.

Week 32 Visit

You will be given a 4 week supply of study drug (ceftriaxone or placebo) along with ursodiol or matching placebo medication at this visit. You will bring your filled-out study diary, unused medication and study drug syringes (empty and un-used) to this visit. During this visit the following procedures and tests will be performed:

- Review of side effects or changes in your condition
- Review of current medications
- Vital signs and weight

- Check of central venous catheter site
- Blood drawn for routine laboratory tests (just over 2 teaspoons)
- Urine collected for routine tests of kidney function
- Additional blood drawn (2 teaspoons) to measure ceftriaxone levels
- Vital capacity test (VC) to check breathing capacity
- ALS Functional Rating Scale, Revised (ALSFRS-R)
- ALS Specific Quality of Life Questionnaire (ALSSQOL)
- Strength testing of arm and leg muscles

These same procedures will be performed every sixteen weeks at Week 48, 64, 80, 96, 112, 128 and 144 Visits.

Final Study Visit

You will bring your filled-out study diary, unused medication and study drug syringes (empty and un-used) to this visit. Some or all of the following procedures may be performed:

- Review of side effects or changes in your condition
- Review of current medications
- Vital signs and weight
- Check of central venous catheter site
- Blood drawn for routine laboratory tests (just over 2 teaspoons)
- Urine collected for routine tests and tests of kidney function
- Vital capacity test (VC) to check breathing capacity
- ALS Functional Rating Scale, Revised (ALSFRS-R)
- ALS Specific Quality of Life Questionnaire (ALSSQOL)
- Strength testing of arm and leg muscles
- Complete physical exam

Other procedures may be performed or additional safety laboratory tests may be drawn (including coagulation studies) at visits, based on medical necessity, as determined by the Site Investigator or other physician.

When the study is complete or when you end your participation, the study team will facilitate your transition to the care of the physician of your choice. If you wish, you may receive your care at The ALS Center at Emory.

Catheter Removal:

When you have stopped taking the study drug permanently, the catheter will be removed. The catheter may also need to be removed during the study if the catheter becomes infected or stops working correctly. The catheter will be removed by a doctor or Nurse Practitioner who specializes in either Surgery, Interventional Radiology, or who is otherwise qualified to remove the catheter.

Catheter Removal Process:

- An antiseptic will be put on your skin around the catheter site to clean bacteria from the skin.
- An injection of medication to numb the area at and around the exit site will be given. This will produce some discomfort from the needle prick and a temporary burning feeling when the medication is given. The area will become numb within a minute or two.
- The doctor will then separate the skin and other tissue near the exit site from the catheter. This is the area under the skin that has grown into the cuff holding the catheter in place.
- Rarely, a small incision may need to be made in the skin to allow the doctor to better reach this cuff. The sensation of releasing the tissue will produce a feeling of pressure.
- When the catheter is released from the skin, the doctor will pull back the catheter until it is removed.
- Pressure will be put on the neck area where the catheter entered the vein. This will be held in place for several minutes to prevent bleeding under the skin. The doctor may put a suture or “stitch” at the exit site opening or, if an incision was made, to the incision.
- As needed, medications may be given (including antibiotics), or additional procedures performed, as part of the catheter removal.

Blood Draws

The amount of blood you will have drawn over the entire course of the study will depend on how long (between 1 year and 5 years) you are in the study. The maximum amount of blood that will be drawn over 5 years is 1,050 ccs, which is a little more than giving 2 pints of blood.

Post Treatment Telephone Call

You will be contacted by telephone by the study coordinator 30 days after your Final Study Visit. This phone call will take about 5 minutes. You will be asked questions about any side effects you may have experienced and your overall health since stopping the study drug. You will also be asked about your current medications.

Subject Responsibilities

As a subject in this trial, you have certain responsibilities to help ensure your safety. Please follow these important responsibilities listed below:

- It is very important that you keep all scheduled appointments.
- Take the study drug as prescribed by the study doctor
- Return all empty and unused study drug syringes at each visit
- Store the drug properly

- Report all side effects and medical problems to the study staff
- Complete your study diaries as instructed
- If you decide to stop taking part in the study, you must inform the study doctor or staff **before** you stop taking the study drug. You will still have study visits, where you will perform vital capacity testing, strength testing, and ALS Functional Rating Scale-Revised, even if you stop taking study drug.
- Contact Dr. Glass before starting any new medications or changing current medications. This includes prescription drugs, over-the-counter drugs, and anything else, like herbal remedies. You may not take any other investigational drugs for ALS while you are taking part in this study.

Because there may be a reaction between different drugs, it is important that you tell your doctor (the investigator) if you are on blood thinners. If you are taking blood thinning medication such as coumadin (warfarin), the dose of coumadin may need to be changed while you are receiving ceftriaxone. You should have your blood tested regularly by the physician prescribing your coumadin to make sure you are on the correct dose.

If you require a typhoid vaccination while you are in the study (usually if you are traveling), it is important that you tell the investigator and the doctor giving you the vaccine all of your medications ahead of time. Antibiotics including ceftriaxone can interfere with the development of an adequate immune response to the oral typhoid vaccine. Because of this, you should not take the oral (by mouth) typhoid, and instead you should request (and receive) a different preparation of the typhoid vaccine.

If you receive any IV treatment that contains calcium (such as nutrition through an IV (called "parenteral" nutrition or TPN)), you should let your study doctor know immediately. There have been reports of interaction between these products, which contain calcium, and ceftriaxone in babies. Because of this, these products should not be given within 48 hours of ceftriaxone, even in adults.

If you wish to stop the study drug, you should tell Dr. Glass so that he may plan for your continued medical care. Dr. Glass may decide not to enter you in the study or to stop your participation without your permission if he feels that you cannot follow the study plan or if your health is in question. Side effects from the drug or the catheter would be examples of reasons for stopping the study drug. In addition, if certain unexpected effects occur (either harmful or beneficial), the entire study may be stopped.

Risks and Discomforts:

There may be side effects from the study drug that are not known at this time. Your condition may not get better, and it may even get worse, as a result of your being in this study.

Ceftriaxone is FDA approved for the treatment of infection. The usual dose is 2 grams a day for 4 to 6 weeks. Side effects seen in people who have taken ceftriaxone for treatment of infection are listed below. The risks of taking ceftriaxone for more than 4 to 6 weeks are not

known. When similar doses of ceftriaxone than what will be given to subjects in this study were given to baboons for 26 weeks, some of the baboons experienced kidney problems and gallstones. At much higher doses of ceftriaxone than what will be given in this study, some of the baboons developed severe kidney damage, which caused kidney failure. Taking ceftriaxone for more than 6 weeks may increase your risk of kidney problems. We will test your blood and urine frequently to check for signs of kidney problems, and you will have abdominal ultrasounds to check for gall bladder problems.

There may be other risks of taking ceftriaxone that have not been seen in people treated for infection. Since ceftriaxone has not been tested in people with ALS, other unexpected side effects may occur. There may be risks of drug interactions causing side effects when people are taking both ceftriaxone and riluzole.

The most serious side effects of receiving ceftriaxone are described below:

DIARRHEA

Diarrhea occurs in a small number of patients treated with ceftriaxone. You should contact your doctor right away if you develop diarrhea. The diarrhea associated with ceftriaxone may or may not be caused by an infection. When it is not caused by an infection, it is called antibiotic-associated diarrhea. People that get antibiotic-associated diarrhea sometimes have had this in the past with other antibiotics. They usually have frequent, loose stools. It can be treated with over-the counter medications, such as Imodium and increasing your fluid intake (water, Gatorade).

***C. DIFFICILE* DIARRHEA**

When the diarrhea is associated with an infection, it is usually caused by a bacteria called *C. difficile*. The symptoms of *C. difficile* diarrhea are frequent, watery diarrhea, fever, nausea, loss of appetite and stomach cramping. If you have these symptoms, call Dr. Glass immediately at 404-778-3807 (After hours: 404-778-5000). If you develop these symptoms, your doctor will check your stool for the infection. You will be treated with an antibiotic called metronidazole, or another appropriate medication, for 14 days. The diarrhea should stop after four or five days of being on the metronidazole. If *C. difficile* diarrhea is not treated early, it can cause dehydration or more serious side effects (including pseudomembranous colitis, see below). Depending on how serious the infection is, you may have to stop the study drug for a short time or permanently.

PSEUDOMEMBRANOUS COLITIS

The most serious side effect of ceftriaxone is pseudomembranous colitis. It is a result of an infection from *C. difficile* (see above). The symptoms of pseudomembranous colitis are high fever (103-105°F), watery or green diarrhea and stomach cramps. If you have these symptoms, call Dr. Glass IMMEDIATELY at 404-778-3807 (After hours: 404-778-5000). Your doctor will admit you to the hospital for treatment. You will be treated with a different type of antibiotic and will need to be examined by a stomach/colon doctor.

Pseudomembranous colitis is a medical emergency and can be life-threatening if is not treated early. Most cases can be treated with discontinuation of the antibiotic (ceftriaxone) and treatment with one of several other medications including oral metronidazole or oral vancomycin. Pseudomembranous colitis can cause chills and rapid heartbeat, and severe cases can result in dehydration or electrolyte abnormalities. In very serious rare cases, it can cause toxic megacolon (a painful condition where the colon becomes enlarged) or colonic perforation (a hole in the colon) and can result in death.

SUPERINFECTION OR ANTIBIOTIC-RESISTENT INFECTIONS

When an antibiotic is used for a long time, the bacteria that live on the person's skin and in the body sometimes become resistant to that antibiotic. When this happens, the antibiotic is no longer helpful. The long term use of ceftriaxone may lead to the growth of bacteria that are resistant to ceftriaxone and other antibiotics in the same family of medicines known as cephalosporins. This means that after being on ceftriaxone for a long time, your body can get infected with bacteria that can no longer be treated by ceftriaxone, or possibly by other cephalosporins (antibiotics in the same group as ceftriaxone). This condition may last your whole life and means that any infection you develop would have to be treated with a different type of antibiotic. It is also possible that this resistance could lead to an infection that is difficult or impossible to treat.

KIDNEY PROBLEMS

Occasionally treatment with cephalosporins (antibiotics in the same group as ceftriaxone) can cause kidney problems. You may develop irritation of the kidneys (acute allergic interstitial nephritis) or lack of blood supply to the kidney (acute tubular necrosis). Both of these conditions can lead to kidney failure. If you have kidney failure, you will require dialysis (mechanical process that replaces kidney function), either temporarily (if the kidney failure resolves) or for the rest of your life (if the kidney failure is permanent). If kidney failure is untreated, it can be fatal.

GALL BLADDER PROBLEMS

The overall rate of gall bladder sludge or gallstones in STAGEs 1 and 2 of this study was 26%. Gall bladder sludge is a mixture of substances inside the gallbladder or ducts. Symptoms of gall bladder sludge or stones include pain in the abdomen, nausea, vomiting, fever and jaundice (yellowing of the skin, due to an excess substance called bilirubin in the blood). Gall bladder sludge and gallstones can be treated with medication. Sometimes, treatment of gall bladder problems requires surgery.

Data from STAGE 1 and 2 of this study, suggested that ursodiol, a medication that you will receive along with the study drug if you are selected to receive ceftriaxone, was helpful in management of these types of gall bladder problems, and was safe and well tolerated.

You will have abdominal ultrasounds performed before receiving study drug and at Week 4, Week 8, and Week 20 to look for gall bladder sludge or stones, or more frequently if you

have symptoms of gall bladder disease. If you develop symptoms and gall bladder sludge or gallstones, the study drug may be stopped temporarily while you receive treatment for the gall bladder disease. You may be seen by a specialist in gall bladder disease to determine the best treatment options.

PANCREATITIS

Gallstone pancreatitis has been reported with Ceftriaxone therapy.

The most frequent side effects due to ceftriaxone include:

- Diarrhea
- Pain and cramping in the stomach area and
- Yeast infections in the mouth and tongue (oral candidiasis) and in women, vaginal yeast infection and itching in the vaginal area

Less frequent side effects include:

- Nausea
- Joint pain and fever
- Low blood white cell count – this may make a person at risk for certain types of bacterial infections
- Pain in the area where the drug is given
- Fever
- Allergic reaction (rash, itching, hives and difficulty breathing)
- Loss of appetite
- Blood conditions, including those that decrease your blood's ability to clot, are possible but very rare.

Although seizures can occur with some of the antibiotics in this family of drugs, it is an unlikely event with ceftriaxone.

Risks from Multivitamin Solution

There have been rare reports of the following side effects associated with the multivitamin (MVI) solution that will be used as the placebo treatment: rash, redness of the skin, itching, headache, dizziness, anxiety, double vision, hives, swelling around the eyes and fingers.

Risks from Central Venous Catheter

The risks of the central venous catheter include:

- Infection of skin, near the exit site of the catheter or along the catheter tube

- Infection in the blood (bacteremia) – this can sometimes cause infection of the heart or other parts of the body, which can be very serious. This may require you having the catheter removed.
- Blood clot in the vein or the catheter tube
- Blood clot in the lung
- Puncture of an artery during line placement
- Collapse of the lung (pneumothorax)
- Breakage or accidental removal of the catheter

We will give you individual instructions and written information on catheter care to prevent potential problems and to recognize catheter problems early. Consultation with your medical providers in the study will be available 24 hours a day, 7 days a week. The catheter must be cared for daily to keep it working correctly. If properly cared for, the catheter is designed to last indefinitely. Some serious problems could, however, require that it be removed. Other less serious problems may develop which can be handled with the catheter remaining in place. If you have an infection or other problem with the catheter, the catheter may have to be replaced one or more times during the study. This involves a surgical procedure to remove the original catheter and a repeat of the catheter placement procedure to implant a new catheter. If the catheter never becomes infected and there are no other problems with the catheter, it is possible that the catheter may remain in place for two years or more. Some risks are more likely to occur during different time periods that the catheter will be in place.

Early problems (during or in the weeks following catheter placement) might include:

- Discomfort at the surgical incision site until it heals.
- Puncture of an artery (a hole made in an artery) during placement of the catheter. Problems of puncture are usually local, in the area immediately around the puncture site; however, there is the potential for serious bleeding to occur. This risk is minimized with the use of ultrasound to guide placement of the central venous catheter.
- During the placement procedure air may get into the lung space, causing the lung to partially or completely collapse. A lung collapse may result in admission to a hospital with the need for a chest tube and may result possible serious complications, including death.
- Infection of the wound where the catheter comes out of the chest. This type of infection may be controlled with oral or intravenous antibiotics. Admission to a hospital may be necessary if the infection is serious.
- As with any surgical procedure, some chest wall discomfort from the placement of the catheter is to be expected. You should let your study doctor know if this discomfort or tenderness is severe or lasts longer than expected.

The following potential risks occur more often when the catheter is in place for a long time:

INFECTION: Long term placement of catheters can be complicated by the development of a local infection at the site of catheter entry (cellulitis). This can present with redness, fever, or pain. An infection can occur along the blood vessel. This is known as septic phlebitis. Both cellulitis and septic phlebitis can be associated with an infection of the bloodstream. This can cause fever, chills, a drop in blood pressure, overwhelming infection known as sepsis, and in some cases can infect the heart causing an infection known as endocarditis. In serious cases this can lead to death. At the first sign of infection of the catheter or catheter site, blood cultures are obtained and appropriate antibiotics are begun. In most cases, the catheter will need to be removed. It can be replaced when the infection has been properly treated. If you have the symptoms of one of these infections, you will be referred to an infectious disease doctor for evaluation.

BLOOD CLOTS: Blood clots can occur during use of a central line. While this problem can be fixed using a medication to dissolve the clot, the risk of developing another clot increases after developing the first one. The use of medication to dissolve the clot also increases the risk of bleeding during this clearing procedure. Blood clots inside the catheter can extend into the vein and cause a blood clot in the vein or break off to cause a blood clot in the lung or other organs. Blood clots left untreated can cause serious or life-threatening problems, and can lead to death. If blood clots develop in the vein or go to the lung, the catheter will be removed to decrease the risk of new ones developing. You may need to take medications that thin the blood for several months. Swelling of the arm, neck or face that can result from a blood clot in the vein may continue for several months or even longer.

CATHETER BREAKS: Though the catheter is designed to last indefinitely, cracks or breaks in the catheter may occur as the catheter ages. Most often, this occurs in the tubing that extends outside the body. This is a more common problem and repair kits can permanently fix it. However, with a break in the catheter there is an increased risk of an infection developing inside the catheter. There is also the rare potential for the air to get in the blood. If large amounts of air get into the blood stream it is an emergency that requires hospitalization.

Risks related to catheter removal include:

- Infection
- Bleeding or bruising in the area of the exit site or where the catheter was under your skin
- Discomfort
- Allergic reaction to the numbing medication or skin antiseptic
- Inability to remove the catheter without the addition of a new skin incision
- Air getting into the chest cavity causing a partial or complete collapse of a lung
- Breakage of the catheter resulting in part of the catheter remaining in the body or blood stream.

Risks from Exposure to X-Rays (Radiation)

This research study involves exposure to radiation from fluoroscopy during the placement of the central line and a chest x-ray after to verify that it is in the right place. This procedure is routinely used for medical purposes. These procedures may not be necessary for your medical care and may occur only as a result of your participation in this study. The radiation dose that you will receive is equal to or less than the natural environmental radiation the average person receives in the United States annually. The principal risk associated with a radiation dose is the possibility of developing a radiation-induced cancer later in life. The risk for radiation-induced cancer from this study is minimal. The risk from radiation exposure of this magnitude is considered to be comparable to other everyday risks. You may receive radiation exposure from the fluoroscope that produces pictures of your internal organs. Your soft tissue and bones will receive a radiation exposure, but the highest radiation exposure will be to your skin. Very high skin exposures can cause reddening of the skin, blistering and even ulceration. Sometimes this will be delayed for weeks or months after exposure. If you should experience skin discomfort in the area that was pictured, report this to the study doctor or your personal physician.

Risks from drawing blood and placement of the central venous catheter:

- Slight pain, a bruise, and/or bleeding where the needle is inserted
- Feeling faint
- Rarely, an infection may develop, which can be treated

Risks from Local Anesthetics

A small amount of medication to numb the skin for the catheter placement will be used. The numbing medication is called lidocaine. You will not be able to sense pain, hot and cold for a few hours after it is injected into your skin. Some people are allergic to lidocaine and other drugs in its class. If you are allergic to lidocaine, bupivacaine, etidocaine, mepivacaine, prilocaine or ropivacaine, you must tell the study staff before having the central venous catheter placed. The risks of lidocaine are an allergic reaction, irritation, pain, numbness that lasts a long time, tingling and swelling at the area where it is injected.

Risks from Breathing (Vital Capacity) and Muscle Strength Testing:

- Feeling tired (fatigue)
- Muscle cramps

Risks from Completion of Questionnaires

You will be asked to complete questionnaires during some of the study visits. These questionnaires ask about your quality of life and ability to carry out certain daily activities. You may feel upset when answering these questions. Although we hope you answer all of the questions, you may skip over any question you do not want to answer.

Pregnancy Risks

If you are a woman: to protect against possible side effects of the study drug, women who are pregnant or nursing a child may not take part in this study. If you become pregnant while taking the study drug, you should tell Dr. Glass right away. The effects of ceftriaxone on an unborn child are unknown; therefore if you become pregnant you will need to stop study drug.

If you are a woman who can become pregnant, you must not be pregnant and/or currently nursing a child. This means you must actively use effective birth control measures during the entire study. Effective birth control includes:

- Abstinence (not participating in sexual activity that may cause pregnancy)
- Hormonal Birth Control
 - Oral Birth Control Pills
 - Implanted or Injected birth control agents (Norplant, for example)
 - Other hormonal birth control (Patch or Ring, for example)
- Intrauterine Device (IUD) in place for at least 3 months before screening
- Condom AND Spermicide
- Another adequate method (as determined by steering committee member review)

If you are a man: the effect of the study drug on sperm is not known. To protect against possible side effects, if you are a man you should not get a sexual partner pregnant while taking the study drug.

The study doctor will discuss birth control methods with you before you start taking the study drug. The study drug must be kept out of the reach of children or anyone else who may not be able to read or understand the label. Do not let anyone else take the study drug besides you.

Benefits:

At this time it is not known if the study drug will provide any benefit to you. It is hoped that ceftriaxone will slow the rate of progression of ALS. The knowledge gained from this study may be of future benefit to you and others with ALS.

Alternatives:

You do not have to participate in this study to receive care for your disease. There are other clinical research trials available to patients with ALS. The study doctor can discuss with you any other trials open for enrollment at this time. Whether or not you choose to participate in a clinical trial will not affect your care at Emory.

Confidentiality:

Certain offices and people other than the researchers may look at your medical charts and study records. Government agencies, Emory employees overseeing proper study conduct may look at your study records. Study sponsors may also look at your study records. Those with the right to look at your study records include

- National Institutes of Health (NIH)/National Institute of Neurological Disorders and Stroke (NINDS) – (the government agency funding the study)
- The NIH Data Safety Monitoring Board – (committee reviewing study conduct, progress, enrollment and safety data periodically for any safety concerns)
- The Food and Drug Administration–(the government agency that oversees drug development & INDs <Investigational New Drug Applications>)
- Health Canada (the Canadian government agency that oversees the patient safety issues in human research for studies conducted in Canada)
- The Office for Human Research Protection-(the government agency that oversees protection of human research subjects)
- Representatives of the Massachusetts General Hospital Neurology Clinical Trials Unit (the academic group conducting the study and the group managing the information (data) from the study)
- Representatives of the Massachusetts General Hospital Biostatistics Department, Boston, MA (the academic group responsible for the data analysis for the study)
- Representatives at The State University Of New York (SUNY) Upstate Medical University (representatives managing the outcome measures and training personnel for the study, and for monitoring study data to make sure it is complete and accurate))
- Representatives at the Tufts University School of Medicine Laboratory – (representatives receiving your coded Ceftriaxone plasma level samples for analysis)
- Dr. Glass and Ceftriaxone clinical trial research staff at Emory.
- The Institutional Review Boards at the Massachusetts General Hospital and Emory – (committees that make certain that your rights are protected)
- The Emory University Office of Research Compliance and the Emory University Office of Clinical Research-(representatives of Emory University responsible for overseeing all research activities)
- Representatives at ICON Laboratories (the group responsible for processing, analyzing and reporting the results of the coded blood and urine samples)
- Members of the ceftriaxone clinical trial Steering Committee (the committee overseeing the progress of the trial)
- The Medical Monitor of the study – a doctor who reviews coded data on a monthly basis for safety concerns
- A doctor who specializes in kidney problems at Emory who will be involved in the study
- A doctor who specializes in Infectious Diseases at Emory who will be involved in the study

- A doctor who specializes in gastrointestinal problems at Emory who will be involved in the study
- The staff in the Interventional Radiology department who will place your catheter and provide medical care during the catheter placement visit
- The staff in the Radiology-Ultrasound department who will perform your abdominal ultrasound examinations
- Nurses and health care personnel at the company that may be helping you with care for your catheter at home.

Records can also be opened by court order. We will keep your records private to the extent allowed by law. We will do this even if outside review occurs. We will use a study number rather than your name on study records where we can. Your name and other facts that might point to you will not appear when we present this study or publish its results.

If you are or have been an Emory Healthcare patient, you have an Emory Healthcare medical record. If you are not and have never been an Emory Healthcare patient you do not have one. Please note that an Emory Healthcare medical record will not be created for you just because you are in this study.

Emory Healthcare may create study information about you that can help Emory Healthcare take care of you. For example, the results of study tests or procedures. These useful study results **will** be placed in your Emory Healthcare medical record. If you agree to be in this study, a copy of the consent form and HIPAA patient form that you sign will be placed in your Emory Healthcare medical record. Anyone who has access to your medical record will be able to have access to all the study information placed there. The confidentiality of the study information in your medical record will be protected by laws like the HIPAA Privacy Rule. On the other hand, some state and federal laws and rules may not protect the research information from disclosure.

Emory does not control results from tests and procedures done at other places. So these results would not be placed in your Emory Healthcare medical record. And they will not likely be available to Emory Healthcare to help take care of you. Emory also does not have control over any other medical records that you may have with other healthcare providers. Emory will not send any test or procedure results from the study to these providers. So if you decide to be in this study, it is up to you to let them know.

The researchers will review the results of certain study tests and procedures only for the research. The researchers will not be looking at these results to make decisions about your personal health or treatment. For this study, those things include: NONE

In Case of Injury

If you get ill or injured from being in this study, Emory would give/arrange for you to have urgent health care. Here we explain who would pay for this health care:

Would Emory Pay? Emory has not set aside any funds to pay for urgent health care. Also, Emory has not set aside any funds to pay you if you become ill or injured from being in this study. The only exception to this policy is if it is proven that the negligence of an Emory employee directly caused your injury or illness. "Negligence" means the failure to follow a standard duty of care.

Would the Study Sponsor, the National Institutes of Health and Massachusetts General Hospital Pay? The Study Sponsor has not set aside any funds to pay for urgent health care. Also the Study Sponsor has not set aside any funds to pay you if you become ill or injured from being in this study.

If you believe you have been injured by this research, you should contact Dr. Glass at 404-778-3807 during business hours and at 404-778-5000 at all other times. If you need medical treatment for this injury, Emory will assist you in getting treatment as needed. If this is an emergency and you can not get in touch with Dr. Glass or study staff, please seek immediate medical treatment on your own. The cost of such treatment will be billed, in the ordinary way, to you or your insurance company. Any cost over what your insurance company pays will be your responsibility. No other compensation will be covered by the study, including compensation for lost wages, transportation, parking, co-pays, deductibles, or indirect losses.

If you do have insurance, you should contact the insurance provider and tell them you want to be in this clinical trial. Ask them what they will pay for and what they will not pay for.

Compensation:

There may be funds available throughout the study to reimburse you for parking and travel to and from the Emory Clinic.

Costs:

The study drug (ceftriaxone or placebo), and all study tests will be provided to you free of charge while you are actively participating in the clinical trial. All supplies including ursodiol will be provided free of cost. Placement of the central line will be provided to you without cost. The costs of other treatments, including care for your ALS, are the responsibility of your insurance company or you directly.

Questions

Contact Dr. Glass at 404-778-3807 during business hours or at 404-778-5000 at other times:

- if you have any questions about this study or your part in it,
- if you feel you have had a research-related injury or a bad reaction to the study drug,
or
- if you have questions, concerns or complaints about the research

If you have questions about your rights as a research subject or if you have questions, concerns or complaints about the research, you may contact the Emory Institutional Review Board at 404-712-0720 or 877-503-9797.

New Information

It is possible that the researchers will learn something new during the study about the risks of being in it. If this happens, they will tell you about it so you can decide if you want to continue to be in this study or not. You may be asked to sign a new consent form that includes the new information if you decide to stay in the study.

Voluntary Participation and Withdrawal:

Your participation is completely voluntary and you have the right to refuse to be in this study. You can stop at anytime after giving your consent. This decision will not affect in any way your current or future medical care or any other benefits to which you are otherwise entitled.

The study doctor/investigator and/or sponsor may stop you from taking part in this study at any time if they decide it is in your best interest, or if you do not follow study instructions.

We will give you a copy of this consent form to keep.