CAROLINAS HEALTHCARE SYSTEM
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Clinical Trial of Ceftriaxone in Subjects with Amyotrophic Lateral Sclerosis (ALS): Stage 3

INTRODUCTION

Dr. Elena Bravver and her associates are asking you to participate in this research study of ceftriaxone at Carolinas ALS / Neuromuscular Center and Carolinas HealthCare System (CHS). You are being asked to take part because you have been diagnosed with amyotrophic lateral sclerosis (ALS). The purpose of this study is to evaluate the safety and effect of ceftriaxone treatment in ALS. You will be one of approximately 30 people involved in this research project at CHS, and your participation will last for at least 52 weeks and up to 5 years.

BACKGROUND

It is known that 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, meaning the FDA has not yet approved its use for this purpose. 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.

HOW THE STUDY WORKS

This study is part of a larger research study being done in three Stages. The first two Stages (Stages 1 & 2) have been completed and data from these stages has been used to evaluate the safety of Ceftriaxone as well as determining the dose that will be used in Stage 3. This study that you are participating in is the last stage (Stage 3) and will test the safety and efficacy (if it has an effect) of ceftriaxone in subjects with ALS.

At the end of the study, a total of 600 subjects will have participated in the study at up to 70 sites across the US and Canada (60 of these subjects will have participated in the previous Stages). We plan to enroll about 30 subjects with ALS for the study at Carolinas Neuromuscular / ALS Center.

Subjects will participate in this study until the last subject enrolled has been in the study 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 Carolinas ALS / Neuromuscular Center.

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.

If you are selected to receive ceftriaxone as your study drug, you will also receive a medication (ursodiol) in the form of a capsule that you will take orally (by mouth) 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) in the form of a capsule that you will take orally two times a day. This placebo medication will look like ursodiol, but will contain no active drug. .

During Stage 3 (the stage in which you are entering the trial), you 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

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Being randomized means that you are put in a group by a chance process, like flipping a coin. You won't know what group you are in and neither will your doctor. We are using this method because it is not clear at the present time which treatment is better. Your chance of receiving each treatment is two in three, or 67%. That means that you have 2 out of 3 chances of getting ceftriaxone and 1 out of 3 chances of getting placebo.

Although you and your doctor will not know which treatment you are receiving, this information can be determined in the event of an emergency. If you have problems that might be related to the study drug, your doctor may "break the code" to find out which group you are in. You would then no longer be in the study.

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 two to four 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
- Evaluation of inclusion and exclusion criteria
- Review of medical history
- Complete physical exam
- Vital signs (blood pressure, heart and respiratory rates, temperature) and weight
- Review of current medications
- Blood drawn for routine laboratory tests such as complete blood count, serum (blood) electrolytes, glucose (blood sugar), for example. (about 2 teaspoons)
- For women able to have children, blood drawn for pregnancy test (1 teaspoon)
- Urine collected for routine tests such as kidney function
- Vital capacity test (VC) to check breathing capacity
- Abdominal ultrasound to check for gallbladder disease (ultrasound may require a separate visit)
- ALS Functional Rating Scale, Revised – ALSFRS-R (a questionnaire about ability to function in certain daily activities)
- Complete ALS Specific Quality of Life Questionnaire (ALSSQOL)
- Strength testing of arm and leg muscles

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 be required to have nothing to eat or drink six to eight hours before this exam. 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 (study doctor), Dr Bravver or Dr Brooks, or research nurse coordinator 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 CMC-Mercy. 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 4-6 hours. Fasting for 6-8 hours is required for catheter placement also. Except in rare cases, this visit will not require an overnight stay in the hospital.

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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 on your neck 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. As part of the catheter placement, you may also be given medication, including antibiotics.

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 two 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

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with tape to prevent the dressing from getting wet. If the dressing does get wet, is 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, the research nurse coordinator 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 fever or infection. The visit may be over the phone, 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 there are signs of infection such as redness, swelling, or puss at the site), 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. If baseline is delayed more than 28 days after screening, the screening visit may need to be repeated. 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 **4 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
- 3 hour observation after receiving study drug

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.

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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 study drug, change catheter dressing and connector. You will have time to practice on our model and ask questions. Education may require a separate visit because it can take 1-2 hours. 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 your filled-out study diary, any unused medication and study drug syringes (empty and unused) with you at each study visit. A nurse may visit you in the home if the site investigator Elena Bravver, MD feels that this is medically necessary.

At this visit you will also receive a bottle of ursodiol or placebo medication. You will take one capsule of 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 Carolinas ALS / Neuromuscular Center each week for the next two weeks, and then every 4 weeks.

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Week 1 and Week 2 Visits

These study visits will each take about 1-**2 hours**. During these visits, the following procedures will be done:

- Review of side effects or changes in your condition and 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 (the giving of) 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 at this visit. You will bring your filled-out study diary, unused ursodiol/placebo capsules and study drug syringes (empty and unused) to this visit. During this visit the following procedures and tests will be performed:

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

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- 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
- Dispense study drug
- Abdominal Ultrasound*

Week 8 Visit through End of Study:
Following the Week 4 Visit, you will return to Carolinas Neuromuscular / ALS Center every 4 weeks until the Final Study Visit. The Final Study Visit will be based on the date the last subject enrolled has been in the study for 52 weeks (one year).

These visits will each take about 2 hours. We will give you a 4-week supply of the pre-filled frozen syringes of study drug (ceftriaxone or placebo) along with a bottle of ursodiol/placebo capsules at each visit. You will bring your filled-out study diary, unused capsules and study drug syringes to these visits. 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 and tests of kidney function

In addition, the following procedures will be performed at weeks 16, 32, 48, 64, 80, 96,112, 128, and 144:

- Weight
- Vital capacity test (VC) to check breathing capacity
- Strength testing of arm and leg muscles
- ALS Functional Rating Scale, Revised (ALSFRS-R)
- ALS Specific Quality of Life Questionnaire (ALSSQOL)
- Blood draw for Ceftriaxone Plasma Level, the portion of the blood that contains proteins, glucose, clotting factors, and minerals (just over 1 teaspoon)

In addition the following procedure will be performed at weeks 16 and 52:

- Complete physical exam

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In addition, the following procedure will be preformed at weeks 24, 40, 56, 72, 88, 104, 120, 136, and 152:

- ALS Functional Rating Scale, Revised (ALSFRS-R)

In addition, the following procedure will be preformed at weeks 8 and week 20:

- 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, additional abdominal ultrasounds may be required. If you have had your gall bladder out prior to this study, your schedule for abdominal ultrasounds will vary from this schedule.

At the **FINAL STUDY VISIT,** you will bring your filled-out diary, unused ursodiol/placebo capsules and study drug syringes and 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
- 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 questionnaires (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 tests) at visits, based on medical necessity, as determined by the study doctor. Additional visits may be necessary for safety monitoring.

It is very important that you keep all scheduled appointments. It is also very important that you contact Dr. Elena Bravver or the research nurse coordinator 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.

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If you have side effects during the study, you should tell the researchers so that they may change the dose of the study drug you are taking or stop the study drug. If you become pregnant while taking the study drug, you should tell Dr. Elena Bravver or the research nurse coordinator right away. You will have to stop the study drug if you become pregnant because there may be a risk of harm to your unborn child.

If you choose to discontinue study drug at any time during the study, we will ask you a question regarding which treatment (ceftriaxone or placebo) you think you were assigned. You have the option to answer or not to answer this question.

If you have to stop taking the study drug early, we would like for you to continue to participate in the study for outcome measures. Outcome measures includes phone calls every 8 weeks for ALS Functional Rating Scale, Revised (ALSFRS-R) and visits to the clinic every 16 weeks for Strength testing of arm and leg muscles, Vital capacity test (VC) to check breathing capacity, and ALS Specific Quality of Life questionnaires (ALSSQOL).

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.

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. In addition, the study staff may ask your permission to call you once or twice, up to 5 years after you discontinue study drug, to enquire about your status.

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 1,050ccs, which is a little more than giving 2 pints of blood.

RISKS
This study has several risks. First, you may be in the placebo (inactive medication) group and have no active medication for your condition. Second, it is possible that you will get the new treatment but do less well than you have been doing. Third, because the treatment is new, we may not yet know all the side effects: something unexpected could happen.

RISKS FROM CEFTRIAXONE
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 patients 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 or gall bladder problems. We will test your blood and urine frequently to check for signs of kidney problems, and you will have frequent abdominal ultrasounds to check for gall bladder problems.

As with all medications, side effects may include allergic reaction. Allergic reactions may range from minor itching or rash to major reactions which can result in death.

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.

Likely:

- 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 Likely:

- Joint pain and fever
- Nausea
- 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

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.

Rare but serious:

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 study 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. Elena Bravver IMMEDIATELY at our 24-hour call line: 1-800-924-7620. 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 pseudo membranous 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 pseudo membranous colitis. It is a result of an infection from *C. difficile* (see above).

The symptoms of pseudo membranous colitis are high fever (103-105°F), watery or green diarrhea and stomach cramps. If you have these symptoms, call Dr. Elena Bravver IMMEDIATELY at our 24-hour call line: 1-800-924-7620. 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.

Pseudo membranous 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. Pseudo membranous 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 mega colon (a painful condition where the colon becomes enlarged) or colonic perforation (a hole in the colon) and can result in death.

If you are diagnosed with pseudo membranous colitis you will have to stop the study drug permanently.

Superinfection or antibiotic-resistant infections

When an antibiotic is used for a long time, it can cause the bacteria that live on a person's skin and in the body to become resistant to that antibiotic. When that happens, the antibiotic is no longer helpful in treating infections. 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.

Rarely, kidney stones (nephrolithiasis) have been seen in people who are taking Ceftraixone. These are generally treatable.

Gallbladder problems

The overall rate of gallbladder sludge or gallstones in STAGES 1 and 2 of this study was 26%. Gallbladder sludge is a mixture of substances inside the gallbladder or ducts. Symptoms of gallbladder 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). Gallbladder sludge and gallstones can be treated with medication. Sometimes, treatment of gallbladder 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 gallbladder problems, and was safe and well tolerated.

You will have abdominal ultrasounds at week 4, week 8, and week 20 to look for gallbladder sludge or stones, or more frequently if you have symptoms of gallbladder disease. If you develop symptoms and gallbladder sludge or gallstones, the study drug may be stopped

temporarily while you receive treatment for the gallbladder disease. You may be seen by a specialist in gallbladder disease to determine the best treatment options.

Pancreatitis
Pancreatitis if inflammation or infection of the pancreas. Gallstone pancreatitis has been reported with Ceftriaxone therapy. The symptoms of pancreatitis include abdominal pain, nausea, vomiting, and fever. If you have symptoms, call Dr. Elena Bravver at 1-800-924-7620 immediately. Your doctor may admit you to the hospital for treatment.

Reproductive risk
You can not be pregnant and/or breast feeding while taking the study drug. If you become pregnant while taking the study drug, you should tell Dr. Bravver right away. The effects of ceftriaxone on an unborn child are unknown. If you are a woman who is able to have children, you must have a negative pregnancy test before starting the study drug. Also, we require you to use an effective method of birth control for at least one month before starting the study and all during the study. Approved birth control methods include:

- 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 (determined by steering committee member review).

As with all medications, side effects may include allergic reaction. Allergic reactions may range from minor itching or rash to major reactions which can result in death.

If you have problems that might be related to the drug, your doctor may "break the code" to find out which group you are in. The physician may only request to "break the code" for medical reasons and this would end your participation in the study.

Risks from pediatric multivitamin solution (placebo)
There have been rare reports of the following side effects associated with the pediatric 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 swelling of the fingers.

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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 research team 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 another 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) include:

- There will be some 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 in 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 can occur more often the longer the catheter is in place include:

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 a long time, 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)
You will have a chest X-ray to check the placement of the central venous catheter. Additional X-rays may be done at any time if we think there is a problem with the catheter. The chest X-ray will expose you to 8 millirem (mrem) of radiation. A millirem (mrem) is way we measure the amount of radiation. This amount of radiation is equal to about 3% of the annual background radiation one is exposed to each year from the earth and the sky.

If we use fluoroscopy to guide the placement of the central venous catheter, you will be exposed to some additional radiation, measured as 230 mrem. This additional exposure is a little over 2/3 of the amount of exposure the average person in the US gets in one year (300 mrem) from background radiation (radiation from their surroundings).

Risks from drawing blood and placement of an intravenous catheter

The risks of drawing blood and placement of an intravenous catheter include:
- Slight pain, a bruise, and/or bleeding where the needle is inserted
- Feeling faint

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- 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, bupivicaine, etidocaine, mepivicaine, prilocaine or ropivicaine, 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
The risks and discomforts of the tests of breathing and muscle strength include:
- 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.

EXCLUSION CRITERIA
You cannot take part in this study if you:
- Are dependent on mechanical ventilation (invasive or non-invasive, including Continuous Positive Airway Pressure (CPAP) or Bilevel Positive Airway Pressure (BiPAP) for any part of the day or night prior to the screening visit
- Had exposure to ceftriaxone of any other cephalosporin within 30 days prior to the screening visit
- Are allergic to Penicillin or any beta lactam or other cephalosporin antibiotics, such as Ancef, Keflex, Ceclor, Ceftin, Lorabid, Suprax, and Fortaz. (Includes mild rash)
- Have a history of known sensitivity to bile acids or ursodiol
- Had exposure to any other investigational agent within 30 days of the screening visit
- Have a known immune compromising illness or therapy
- Have active gastrointestinal disease within 30 days of the screening visit

- Have a history of antibiotic-induced colitis
- Have a history of drug abuse or alcoholism
- Have active biliary disease, including gallstones
- Any unstable medical conditions including heart, lung, kidney, liver, small organs/glands, hormones, blood, or active infectious disease, or current malignancy
- Have unstable psychiatric illness defined as psychosis or untreated major depression within 90 days of the screening
- Have Laboratory Values out of the normal limit ranges at screening visit
- Women of childbearing potential not practicing adequate contraception
- Have a history of known sensitivity to bile acids or ursodiol

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.

BENEFITS

This study may or may not improve your condition. The information gained from your case may benefit others with ALS.

ALTERNATIVE PROCEDURE/TREATMENT

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 Carolinas ALS / Neuromuscular Center.

There is currently no known effective therapy for ALS. Riluzole, a drug that slows the release of glutamate, 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 14 days before the screening visit and at least 30 days before they can start the study drug.

ADDITIONAL COST

The study drug (ceftriaxone or placebo and ursodiol or placebo) , and all study tests will be provided by the Sponsor, the National Institute of Health and National Institute of Neurological Disorders and Stroke, without cost to you or your insurance company while you are actively participating in the clinical trial. Placement of the central line, including the chest x-ray, will be provided to you by the Sponsor without cost. If the ALS home health nurse performs a home visit in relation to the study (for example, catheter care, infusion training, etc) this visit will be provided free of charge. The costs of other treatments, including care for your ALS, are the responsibility of your insurance company or you directly.

COMPENSATION

In the event that you are harmed as a result of your participation in this study (please refer back to the risk section), we will provide or arrange for treatment as necessary. If you experience any injury or illness due to your participation in this study, please contact Dr. Elena Bravver or the research nurse coordinator at 1-800-924-7620 right away. If you need medical treatment for this injury, Carolinas ALS / Neuromuscular Center will assist you in getting treatment as needed. If this is an emergency and you can not get in touch with Dr. Elena Bravver or study staff, please seek immediate medical treatment on your own.

This treatment, as well as other medical expenses, will be billed to you or your insurance company in the usual manner. 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, co-pays, deductibles, or indirect losses.

You will receive $50.00 for each completed regular study visit for a possible total of $2,700 . This will include Screening, Baseline, Week 1, 2, 4, 8, and each following 4 week visit up to week 200 for stage 3 of this trial. This compensation will be given at pro-rated intervals (every 3 months) during the study. If you withdraw from the study, your compensation will be prorated for the visits you complete. If you receive over $600 in one calendar year, you may be given additional tax forms.

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WITHDRAWAL

Your participation in this study is completely voluntary. You should feel under no pressure to be in the study. If you decide to not be in the study, that will not in any way harm your relations with your doctors or with Carolinas HealthCare System. You are free to stop being in the study if you change your mind after entering it. This would not harm your relations with your doctors or Carolinas HealthCare System. We will tell you about new medical findings that may affect your willingness to continue in the study.

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

CONFIDENTIALITY

The records of this study will be kept private. In any sort of report that we might publish, we will not include any information that will make it possible to identify a patient. Your record from this study may, however, be reviewed and/or photocopied by the drug manufacturer, by Carolinas HealthCare System, Massachusetts General Hospital and SUNY Upstate University, or by representatives of the Food and Drug Administration or other government agencies. To that extent, confidentiality is not absolute.

AUTHORIZATION

If you wish to take part in this clinical study, you will be asked to sign this consent form. It allows the study sponsor and the study investigator to collect, process and pass on to the sponsor organizations any relevant personal health information collected from you during the study. These are activities routinely carried out during all clinical studies.

You have been told that personal information about you (including sensitive personal health information, such as your medical history and your racial/ethnic origin) will be reviewed, collected on a computer database, stored in electronic or manual files, audited, and/or otherwise processed by:

- the clinical study investigator, Dr. Elena Bravver and research staff,
- the study sponsors, National Institutes of Health (NIH) and National Institute of Neurological Disorders and Stroke (NINDS)

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- 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 oversees drug development & IND)
- Health Canada – (the Canadian government agency that oversees the patient safety issues in human research for studies conducted in Canada)
- regulatory or other governmental authorities of the United States and other countries,
- 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)
- The Institutional Review Board at the Massachusetts General Hospital (the committee that makes certain that your rights are protected)
- 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 ICON Laboratories (the group responsible for processing and analyzing and reporting the results of the coded blood and urine samples for analysis)
- representatives at the Tufts University School of Medicine Laboratory – (representatives receiving your coded ceftriaxone plasma level samples for analysis)
- 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 specialized in kidney problems at Carolinas Medical Center who will be involved in the study
- a doctor who specializes in Infectious Diseases at Carolinas Medical Center
- the staff in the Interventional Radiology department who will place your catheter and provide medical care during the catheter placement visit
- nurses and health care personnel at the company that will be helping you with care for your catheter at home.
- other persons authorized by the study sponsors,
- Carolinas HealthCare System employees,
- other persons or agencies as required by law or allowed by federal regulations,
- EMSI, a laboratory company that may be utilized to draw safety labs at your home if needed

You have been told that your personal data are being collected and processed to:

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- check your suitability to take part in the study,
- monitor your treatment with the study drug ceftriaxone,
- compare and pool treatment results with those of other subjects in clinical studies,
- support the development of the study drug ceftriaxone,
- support the licensing application for regulatory approval of the study drug ceftriaxone as a treatment for ALS in the world and/or support the marketing, distribution, sale and use of the study drug ceftriaxone as a treatment for ALS anywhere in the world.

You have been told that your personal information may be processed within the U.S. or elsewhere in the world or transferred to or from the U.S. for review, processing and/or storage by an associated company or a carefully selected third-party organization. By signing this document, you explicitly consent to the transfer of your personal information, including sensitive personal information, collected during this clinical study, for review, processing and/or storage. Your personal health information may be further shared by the groups above. If shared by them, the information will no longer be covered by the Privacy Rule. However, the groups are committed to keeping your personal health confidential.

You may refuse this authorization to transfer your personal information. If you choose not to agree to this authorization, you might be ineligible to participate in the study. If you decide not to sign this authorization, that will not harm your relations with your doctors or with Carolinas HealthCare System.

You have the right to inspect your medical record at any time. Your research record may be unavailable until the conclusion of the study. At that point, it will be available. Please speak with the study doctor if you desire to access your record.

You have been told whenever your personal information is processed, it will be kept confidential and secure, to the best of our ability. It will be used only for the purpose for which it was collected.

This Authorization does not have an expiration date. You have been told that according to the guidelines for good clinical practice, the study investigator and sponsor will keep your personal information for at least six years. If you do not withdraw the Authorization in writing, it will remain in effect indefinitely. If you wish to revoke authorization to use your personal information, you will notify the study doctor, Elena Bravver, MD, 1010 Edgehill Rd North, Charlotte, NC 28207, 800-924-7620, in writing. Some of the data obtained from your record prior to your revocation may still be used if considered necessary for the study.

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FINANCIAL INTEREST OF THE INVESTIGATOR

None of the doctors asking you to participate in this study have received or will receive money or other benefits for personal use from the sponsor. However, the sponsor will give money or other benefits to a research fund, foundation, educational institution, or other organization with which the doctor or study staff is associated.

QUESTIONS

The researcher doing the study at Carolinas Healthcare System is Dr. Elena Bravver. You may ask her any questions you have now. If you have questions later, you may contact Dr. Elena Bravver. If you feel you have experienced a research related injury or reaction to the study drug, contact Dr. Elena Bravver.

Carolinas Neuroscience and Spine Institute
1010 North Edgehill
Charlotte, NC 28207
Telephone (800) 924-7620

The Institutional Review Board is a group of people who review the research to protect your rights. If you have questions about the conduct of this study or about your rights as a research subject, you may call the chairperson of the Institutional Review Board of Carolinas Healthcare System for information regarding patients' right in a research study. You can obtain the name and number of this person by calling (704) 355-3158.

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CONSENT

I have read the above information. I have asked any questions I had, and those questions have been answered. If I am female, I am not pregnant or nursing and will avoid becoming pregnant for the duration of the study. I will use an acceptable method of birth control to prevent pregnancy. I agree to be in this study and authorize the use of my personal health information. Dr. Elena Bravver will give me a copy of this consent.

_____	_____
Patient [guardian] Print Name	Date/Time
_____	_____
Patient [guardian] Signature	Date/Time
_____	_____
Signature of Person Obtaining Consent	Date/Time
_____	_____
Investigator Signature	Date/Time

Identity of representative:
_____ Next of Kin
_____ Parent/Guardian
_____ Healthcare Power of Attorney

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