INFORMED CONSENT TO TAKE PART IN A CLINICAL RESEARCH STUDY AND AUTHORIZATION TO USE AND DISCLOSE MEDICAL INFORMATION

Sponsor / Study Title:	**Division of Microbiology and Infectious Diseases (DMID), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) / "A PHASE I, OPEN-LABEL STUDY TO ASSESS LUNG PHARMACOKINETICS AND SAFETY OF A SINGLE DOSE OF APRAMYCIN ADMINISTERED INTRAVENOUSLY IN HEALTHY ADULT SUBJECTS"**
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KEY INFORMATION

The following is a summary of the things you should know:

- You are invited to take part in a research study of an investigational drug called apramycin. This means that the drug is evaluated in healthy persons like you and is not approved for use in people by the U.S. Food and Drug Administration (FDA). Your participation in voluntary and your consent is sought after you have read and understood information provided in this document. If you consent to participate and change your mind, you may withdraw from the study and notify the study doctor. If you withdraw after you received a treatment with the study drug, you will be asked to have standard medical physical examination and lab tests to ensure you are doing well and do not need more follow up.

- Apramycin is a compound that is being developed for use as an antibiotic against severe infections that are resistant to multiple available antibiotics. The purpose of the research study is to evaluate how safe it is to give apramycin to people (that is, what type side-effects it might cause and how severe they are), to study its pharmacokinetics (that is, how the body handles the study drug) and if it is taken up by the lungs.

- If you decide to participate, you will be in the study for up to 58 days (from Screening Visit to Final Visit). There is a Screening Period of up to 26 days; a 5-day/4- night in-patient period, with 2 days of screening and baseline tests before you receive the study drug on Day 1; and 3 days of follow up after receiving the study drug; and an out-patient follow-up period of approximately 27 days, with two return visits to the Research site, about 14 days and 30 days after receiving the study drug.

- Screening evaluations include standard physical examination and blood and urine tests, test of lung function, an electrocardiogram (ECG; tracing of the heart signals), ear exams and hearing tests, and may be completed in one or two visits. If you meet all the requirements to take part in the study, you will be admitted in the clinical research unit 2 days before study drug administration to confirm that you continue meeting the requirements to participate in the study. The day before you receive the study drug you will be assigned in one of 5 groups of 4 people each who will have only one bronchoscopy and bronchoalveolar lavage at either 30 minutes (0.5 hours), 2, 4, 8 or 24 hours after receiving the study drug. On Day 1, you will receive a single dose of the study drug in a dose of 30 mg/kg body weight. The study drug will be given in a vein in your arm over 30 min. The effects of the study drug on you will be assessed by vital signs (blood pressure, heart rate, breathing rate and temperature), physical exams and blood and urine at various timepoints after you received the study drug and until your last visit.

- Bronchoscopy with bronchoalveolar lavage is an established procedure to examine the lung airways and take fluid specimens from a segment of the lung. The procedure will be done in the university hospital. An anesthesiologist will give you a small dose of a sedative drug or light anesthesia to minimized discomfort before the procedure. Then, the pulmonologist (a lung specialist) will pass a pneumonoscope (a thin tube with channels to look inside the lung) through your nose down your throat into a segment of your lung and inject and quickly remove for testing small amounts of sterile saline (salt solution). The procedure will take about 10 minutes to complete after you are sedated, and you will then be monitored in the recovery room before you return to the research unit.

- Ear exams and hearing tests are standard procedures and will be performed in the Audiology Department on the hospital campus. Ear exams will consist of looking inside your external ear canal with an otoscope (an instrument with a light source to look into the ear). Hearing tests will be performed in a quiet room and evaluate your responses to sounds of different frequencies and volume transmitted through the air and bone.

- The risks of the study can involve risks caused by the study drug and risks caused by study procedures.
    - In a completed research study in healthy people, apramycin was safe and well-tolerated in doses up the dose to be used in this study. Potential side-effects of apramycin are an allergic reaction, and side-effects reported after multiple doses or

high doses of other aminoglycoside antibiotics, such as decrease in kidney function, hearing loss, imbalance problems and muscle weakness.

- Bronchoscopy with bronchoalveolar lavage is a common and generally safe. Potential side-effects during the procedure include a drop in blood oxygen. increase in heart rate, and irregular heartbeats, which will be monitored continuously, and oxygen or medications may be used. Very rarely, injury to the airway or to the lung with accumulation of air or blood in chest cavity may occur and may require immediate intervention. Other side-effects may include nausea and dizziness from the sedative, and nose and throat irritation, nasal stuffiness, and cough from the pneumonoscope. Very rarely, a syndrome like bronchitis several hours later could occur. You will be followed closely in the recovery room and the research unit and appropriate treatment will be given if you develop any symptoms.
- No side-effects are expected from ear and hearing testing procedures.
- There may be side effects of drawing blood with a needle and/or IV tubes and IV catheter placement. Local pain, bruising, bleeding, inflammation or infection might occur at the site of the needle stick where blood is drawn. There is a possibility of dizziness or fainting while your blood is being drawn. Precautions will be taken to minimize the above complications.

- The study has no direct benefit for you. Knowledge gained in the study could be of future benefit to public health and to individuals with infections, who might benefit if the study drug is licensed. You will be promptly notified of any abnormal clinical test results that may suggest previously unknown abnormalities that could be clinically significant, and you will be counseled to see your doctor for follow up.

- There are no alternatives to the research study. You are free to consent to participate in the study or not to participate or to withdraw after your consented initially. You will be compensated for the study days and procedures you complete. You will not be penalized if you withdraw from the study.

- Your personal health information will be protected. Your study medical record, laboratory test results and storage tubes containing your blood, plasma, urine or bronchoalveolar lavage specimens will be coded and will not identify you by name or provide any other personal information that can identify you.

- You will be asked to consent separately to keep in long-term storage residual plasma or bronchoalveolar lavage samples to be used in future clinical research by the study sponsor, the Division of Microbiology and Infectious Diseases (DMID) of the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH). DMID.

INTRODUCTION

You are being asked to be a subject in a clinical research study. You cannot be in this study if you are in another research study or have been in another study within the past month. Before you

agree to be a part of this study, it is very important that you read and understand the study plan and in what ways you will need to cooperate. This consent form may have words in it that you do not understand. You may ask the study doctor or the study staff to explain any words or information that you do not understand. If you sign and date this form, it means you want to be in this study.

This form describes the reason for the study, and the way the study will be done. It also describes the benefits, risks, discomforts, and warnings about the study. This form will also explain how your medical information will be used, and who may see it. It describes your rights as a subject in the study.

The study staff will ask you many questions. Your answers must be completely truthful. Your health history and any changes in the way you feel during the study are very important. You must tell the study staff about any changes in your health or the way you feel. If you are not truthful, you may harm yourself by being in this study. Your signature and date on this consent form serves as proof of your promise that the information you give is true and correct and that you will remain truthful during this research study.

Alliance for Multispecialty Research, LLC (AMR, LLC.), the Research Site, is being paid by the Division of Microbiology and Infectious Diseases (DMID) of the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH). DMID is also referred to as the "study sponsor" in this document.

BACKGROUND AND PURPOSE:

The study doctor and Division of Microbiology and Infectious Diseases (DMID), the sponsoring drug company, are conducting this research study of an investigational drug called apramycin. An investigational drug is a study drug that is not approved by the U.S. Food and Drug Administration (FDA).

Apramycin, the investigational drug in this study, is a natural drug that was isolated from a fungus cultured in the laboratory and has been used as an antibiotic extensively in the last 40 years for the treatment of animal infections. It belongs to the class of aminoglycoside antibiotics that are used for the treatment of infections in people. It is being evaluated as an antibiotic for use in people because it was found to have some important properties in laboratory testing: (a) it is effective against infections by bacteria that are resistant to treatment by approved antibiotics; (b) it does not interact with genes affected by other antibiotics that cause hearing impairment or loss; and (c) it was safe in animal testing. Because of these findings, apramycin received approval to initiate testing in people by regulatory authorities, such as the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA). In a completed first clinical study in healthy subjects like you, apramycin was tested in doses ranging from 0.3 to 30 mg/kg body and follow up periods up to 30 days and was found to be safe and well tolerated.

This study is being done to evaluate the effect of a single dose of the study drug, apramycin, after it is administered intravenously (IV; in the vein). The overall goals are to determine the safety, tolerability, pharmacokinetics (PK) and buildup of the study drug in the lungs. Pharmacokinetics

is the study of how a drug is absorbed, distributed, metabolized, and eventually eliminated by the body. Apramycin, the study drug, is being developed for the treatment of bacterial infections that are resistant to multiple current antibiotics.

This study will be conducted in subjects that are healthy and between 18 to 45 years of age who are in good health, do not take certain medications, and, for women, if they are not pregnant or breastfeeding. There will be a total of approximately 20 male and female subjects in this study. This study will be done at one Research Site in the United States. All subjects in this study will receive single dose of apramycin on Day 1 of the study.

The study will take up to 58 days to complete and is made up of the following periods: a Screening Period up to 26 days (Day -28 to Day -3), during which you will make up to 2 visits to the Research Site for medical testing and ear and hearing exams; a Check-in day (Day -2) to confirm your eligibility; a Baseline day (Day -1) to assign you to study treatment cohort (group) and enroll you in the study, and complete baseline assessments; an Inpatient Study Treatment Period lasting 3 days/2 nights, with eligibility reviewed prior to study treatment administered on Day 1, bronchoscopy with bronchoalveolar lavage (BAL) done once for each subject within 24 hours after dosing, and in-patient follow up completed on Day 2 and Day 3; and an Outpatient Follow-up Period of 27 days (Days 4 to 30) with two site visits to the Research Site, on Day 14 and Day 30 after study treatment. The last visit will be on Day 30.

A description of this research study will be available on *https://www.clinicaltrials.gov* as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the study results. You can search this Web site at any time.

INFORMATION ABOUT THE STUDY:

If you are eligible to take part in this study, you will receive a dose of apramycin based on your body weight (30 mg for every kilogram). The study drug will be given once by IV infusion over 30 minutes on Day 1 of the study treatment period. Each subject will take the study drug as open label, meaning that you will know that you are going to receive apramycin. Additional subjects may also be admitted to the Research Site before dosing and may serve as back-up study subjects. You may be selected to participate in this research study as either a study subject or a back-up study subject.

After dosing with apramycin, you will have a lung procedure called bronchoscopy with bronchoalveolar lavage (BAL) to measure the amount of apramycin in the lung. Bronchoscopy is done under "conscious" sedation. You continue to breathe on your own but do not feel the discomfort of having the tube in your mouth or nose. It may feel uncomfortable, but it should not hurt. The entire procedure, including prep and recovery time, typically takes about four hours. Bronchoscopy itself usually lasts about 30 to 60 minutes.

Each subject will be assigned to a different time for completing the lung procedure. The lung procedure will be done once in each subject at one of 5 different timepoints between 0.5 hours to 24 hours after dosing. There will be 4 subjects at each timepoint who will have this procedure. This procedure will be done by specialist pneumonologists (lung physicians). Study staff will

accompany you to bronchoscopy and be present during the procedure as needed to collect required information after dosing with study drug.

You will also have several ear exams and audiology tests to evaluate any effects of apramycin on your hearing. Appointments for hearing tests will be made by the Research Site and study staff will accompany you to your appointments.

You will be asked to come to the Research Site 4 times: 2 times before receiving the study drug, and 2 times after receiving it. If it is not possible to complete all testing on some days, or if there is a need to do a repeat test, you will be given an appointment to complete testing on another day. Also, you will be admitted in the Research Site on the same day after you complete testing on the second visit and stay in the AMR clinical trial unit for 4 nights if you meet the requirements for receiving the study drug.

The first visit will be a **screening visit**. You will be informed about the study, have your questions answered and, if you decide to participate in the study, as shown by signing and dating this consent form, you can proceed to the first part of screening to evaluate your eligibility to take part in the study. If you decide to participate, and sign and date this consent form, you will have medical tests and complete an ear and hearing tests.

If you pass the screening tests, you will be asked to return to the Research Site for a second visit (**Day -2, Check-in)** to complete medical and ear exam and hearing tests to confirm your eligibility to be admitted. If you are eligible to continue, you will be admitted to the Research Site on this day (Day -2) and stay overnight. On the next day (**Day -1, Baseline**), your eligibility to enroll in the study will be evaluated before you have electrocardiograms (ECGs). If you are eligible, you will be enrolled and assigned to 1 of 5 study treatment cohorts (groups), T1 to T5, to have only one bronchoscopy with bronchoalveolar lavage (BAL) at a specified timepoint after you receive the study drug as follows: Cohort T1, 0.5 hours (30 min); Cohort T2, 1 hour; Cohort T3, 4 hours, Cohort T4, 8 hours; and Cohort T5, 24 hours. You will be told what your cohort number is. You will complete ECGs on the same day. An ECG is a test to monitor the electrical activity of your heart. If you continue being eligible to continue participating in the study, then you will stay in the Research Site overnight for the inpatient study treatment period.

On the next day (**Day 1**), your eligibility to receive the study drug will be evaluated. If you are eligible to receive the study drug, you will begin the **inpatient study treatment period.** In the morning on Day 1, you will have three baseline ECGs taken before you receive the dose of apramycin. Prior to receiving a dose of Apramycin, you will be required to have no food to eat or drink at least 6 hours. Apramycin, dissolved in 30 mL (about 1 ounce or 2 tablespoons) of sterile normal saline will be slowly administered intravenously (IV) through a vein in your forearm over 30 minutes.

You will be asked for any new symptoms before dosing (taking the study drug) and monitored for any side effects from the time of dosing, before, during and after the lung procedure, and until you complete the last visit (Day 30).

You will have the lung procedure (bronchoscopy with bronchoalveolar lavage) at the time that was assigned to your cohort number after you receive apramycin. You will have no food to eat at least 6 hours before dosing with apramycin and 2 hours after dosing. If you have the lung procedure, you will need to continue the fast until the procedure is completed and 2 hours after the lung procedure. This means that if you are in groups T1, T2, or T3, you will continue fasting until at least 2 hours after the lung procedure; if you are in group T4, you will eat 2 hours after the dose of apramycin, but you will need to start fasting again 4 hours before the lung procedure and continue until 2 hours after the procedure; and if you are in group T5, you will start eating 2 hours after dosing, but fast overnight before the lung procedure in the morning of the next day and for 2 hours after the procedure. You will be allowed to drink water during that time, and you may be given nutritional broth or a light meal, depending on what time after dosing you will have the bronchoscopy.

You will continue to stay at the Research Site overnight for 2 days after dosing for observation and additional required testing. These will include medical examinations, measurements of vital signs (heart rate, blood pressure, respiratory rate, and oral temperature), monitoring of blood oxygen, ECGs, and hearing tests. Blood will be drawn from a vein for clinical laboratory tests and measurements of the study drug at various times up to 60 hours after dosing. Additional testing may be done if medically indicated. You will be discharged from the Research Site on **Day 3**, after completion of the required testing at 60 hours after dosing. You may be kept overnight at the Research Site and discharged in the morning of Day 4 depending on timing of the 60-hour collection.

You will then start the **Out-patient Follow Up Period**. You will return for two out-patient follow up visits to the Research Site, on **Day 14** and **Day 30,** to complete additional required observations. Additional hearing tests will be done on these days. If there is no medical reason for further follow-up, you will complete your participation in the study on Day 30.

The schedule for screening, study treatment and all study periods are shown in the table below:

Outpatient Screening	**Inpatient**		**Inpatient Study Treatment**		**Outpatient Follow Up**	
Screening Period	**Check-in**	**Baseline**	**Dosing**	**Discharge**	**Follow-up Visit**	**Final Visit**
Day -28 to Day -3	Day -2	Day -1	Day 1	Day 3	Day 14	Day 30

MEDICAL MONITORING:

The study staff will monitor you for side effects during your stay in the Research Site and provide medical care as needed if you have any medical problems. Guidelines have been created to evaluate the safety of the study drug and whether the side effects are acceptable.

WHAT WILL HAPPEN DURING THE STUDY?

SCREENING PERIOD (Day -28 to Day -3):

Screening Visit
During this visit, you will be informed about the study, have your questions answered and, if you decide to participate in the study, as shown by signing and dating this consent form. Following consent, you will have your medical assessments completed for the study staff to determine if you are in good health and qualify to continue participation in the study.

After signing and dating this consent and before you begin the study, the following screening tests will be done:

- Complete medical history (including your demographic information) and medication review.
- Vital signs (blood pressure, heart rate, breathing rate and oral temperature) measured. You will need to rest for at least 5 minutes before your vital signs are taken.
- Height and weight measured, and Body Mass Index (BMI) calculated.
- Physical examination.
- 12-lead ECG (standard recording) – This will require attachment of electrodes from the standard ECG machine to your chest, arms, and legs. Male subjects may have to have their chest hair shaved for the ECG. Female subjects may not be allowed to wear a bra during ECG-related procedures.
- Blood and urine collected for laboratory tests (you will be asked to not eat or drink anything other than water for at least 6 hours before blood collection).
- Urine drug screen for marijuana or other illegal drugs. The test must be negative to qualify.
- Alcohol test in the urine. The test must be negative to qualify.
- Cotinine test in the urine (for use of nicotine products).
- Blood collected for serum pregnancy test if female. The test must be negative to qualify.
- Blood collected for measurement of follicle-stimulating hormone (FSH) if post-menopausal female.
- Testing for Hepatitis B, Hepatitis C, and HIV infections: Your blood will be tested for the HIV antibody. HIV is a virus that causes AIDS. You will also be tested for Hepatitis B and C Viruses. All these test results must be negative to qualify for the study. It may take weeks or months after being infected with HIV for the test to be positive. If either of these tests is positive, a confirmation test will be done by the laboratory. If the HIV or hepatitis test are positive, you will be notified by the Research Site and given information on how to follow up for further medical care. As required by law, positive test results must be reported by the Research Site to the State Department of Health. If you have any questions about what information is required to be reported, please ask the study staff. If the Research Site becomes aware during your participation in this study that there is any change in the HIV or Hepatitis Virus results, you will be withdrawn from the study.

- On this or another visit, we will also review the hearing criteria and you will have the following ear exam and hearing tests by an audiologist (a hearing specialist) in a nearby building, where you will be accompanied by study staff:
    - Ear Examination: You will have 4 tests that allow the audiologists to evaluate your external ear canal, the ear drum, the middle ear and the eustachian tube (the canal that connects the middle ear with the upper part of the throat):
        - Ear Otoscopy: inspection of your ear canal with a microscope to magnify the view of the canal and the ear drum.
        - Valsalva test: you will take a deep breath and then blow out fast with your mouth closed, as you do when you pop your ears, while the ear drum movement and middle ear pressure are measured.
        - Tympanometry: is a test of the condition of the middle ear, the mobility of the eardrum and the conduction bones by creating variations of air pressure in the ear canal using a small probe in your ear canal.
        - Stapedial Reflexes: a test of the lowest stimulus that activates the stapedial reflex at various sound pressure levels using a small probe in your ear canal.
    - Ear audiometry: The test evaluates the condition of your inner ear. It evaluates how sharp your hearing is by asking you to detect sound of various frequencies transmitted through the air or bone. The test is done in a quiet room or chamber, and you may wear headphones (for air conduction) or have a probe that sends sounds attached to your head (for bone conduction). It requires your concentration and attention.
    - Distortion product otoacoustic emissions (DPOAEs): This is a test of the condition of the inner ear. This takes a short time to complete and requires the insertion of a small probe in your ear canal.

After you complete the ear and hearing tests, you will return to the Research Site and be told of the results of medical and hearing tests and whether you can continue participating in the study.

- If you do not meet the study requirements, you will be discharged on this day. You will be told why you were not selected for the study.
    - If there is a medical condition or abnormal laboratory test that needs further medical attention, you will be counselled to follow up with your primary physician or contact community physicians or clinics where you can go for testing and follow up. You may sign and date a release form to allow the Research Site to release medical tests to you or send them to your own doctor or clinic.
    - If you did not pass the hearing tests, you will be told why and be counselled to see a specialist. You will be asked to sign and date a release form to obtain a copy of the hearing tests.
- If your medical tests and hearing are good, the study staff will give you an appointment to return to the Research Site to complete the inpatient screening tests to confirm your eligibility to participate in the study.
- You will be told to come prepared to stay for the inpatient study treatment if you pass the tests.

- You will be counselled to avoid pregnancy, use appropriate contraception (both male and female), and avoid prohibited medications, tobacco and other nicotine products, alcohol, and marijuana and or other illegal drugs.
- If you are male, you will be counseled to avoid sperm donation for 30 days after dosing.
- You should avoid strenuous physical activity and exposure to loud noise until you complete the study if you meet the study criteria or until you are told you did not qualify.

CHECK-IN VISIT (Day -2) (2 days before the study treatment period)

On this day, the following procedures will be done:

- Update medical history.
- Review and update prior medications.
- Vital signs (blood pressure, heart rate, breathing rate, oral temperature) measured.
- Weight taken.
- Physical examination.
- 12-lead ECG (standard paper recording).
- Blood and urine samples collected for lab tests (you will be asked to not eat or drink anything other than water for 6 hours before blood collection).
- Urine pregnancy test (for females). The result must be negative.
- Urine drug screen for marijuana or other illegal drugs. The result must be negative.
- Alcohol test in urine. (The result must be negative.)
- Cotinine test in the urine. (The result must be negative.)
- Repeat Ear exam (ear otoscopy) and the Hearing tests (ear audiometry and distortion product otoacoustic emissions [DPOAEs]).
- Review your results of the procedures to see if you still qualify.
    - If you do not meet the study requirements, you will be discharged on this day. You will be told why you were not selected for the study If there is a medical condition or abnormal laboratory test that needs further medical attention, you will be counselled to follow up with your primary physician or contact community physicians or clinics where you can go for testing and follow up. You may sign and date a release form to allow the Research Site to release medical tests to you or send them to your own doctor or clinic.
    - If you did not pass the hearing tests, you will be told why and be counselled to see a specialist. You will be asked to sign and date a release form to obtain a copy of the hearing tests.

If you meet the study requirements, you will be admitted to the Research Site. After you are admitted, you will read the House Rules and are expected to follow them while you participate in the study. You will be encouraged to drink plenty of fluids to keep well hydrated. You will receive dinner and snacks in the Research Site.

INPATIENT BASELINE (Day -1):
You will have the following assessments on this day:

- You will be assigned to one of five study treatment cohorts (groups), T1-T5, that correspond to the timepoint when you will have a single bronchoscopy with BAL after receiving the study drug. You will be told what cohort you were assigned to.
- Update medical history.
- Review and update prior medications.
- Vital signs (blood pressure, heart rate, breathing rate, oral temperature) measured.
- Weight taken.
- Physical examination completed.
- 12-lead standard ECG (standard paper recording) done in triplicate at 4 timepoints during the day that will match the timepoints when you will have ECGs after dosing on Day 1. You will be resting for about 5 minutes while ECGs are recorded.
- Review the results of the assessments to see if you still qualify.
- You will not be allowed to eat anything for 6 hours before taking the study drug the following morning, but you will be allowed to drink water during that period.
- You will be counseled to avoid strenuous exercise and loud music.

INPATIENT STUDY TREATMENT PERIOD (Days 1, 2 and 3)
You will receive the study drug on Day 1 and followed as inpatient until Day 3. The following procedures will be done during this period:

DAY 1: Administration of study drug

Before Dosing:

- You will not eat any food or drink (other than water) at least 6 hours before taking the study drug (dosing). That means that you may have an evening snack the night before dosing but no food afterwards, and you will not eat breakfast before dosing. You will be allowed to drink water during that time before dosing.
- Update medical history.
- Physical exam may be done as needed depending on your symptoms.
- Review and update medications taken.
- Vital signs (blood pressure, heart rate, breathing rate, oral temperature) measured approximately 30 minutes before study treatment.
- 12-lead ECG (standard paper recording) within approximately 30 minutes before study treatment.
- Review the results of the assessments to see if you still qualify to receive the study drug.
- An IV line (a short intravenous catheter) will be inserted in a vein in your hand or forearm to study drug infusion. Another IV line will be inserted in your other arm to draw blood.
- Blood and urine samples collected for lab tests (you will be asked to not eat or drink anything other than water for 6 hours before blood collection).
- Blood drawn for analysis of study drug.
- You will be kept well hydrated by drinking water starting before the study drug infusion and continue until 24 hour later. You will drink about 2 liters during this period (about 64

fluid ounces or 8 8-ounce glasses). You will be asked to document the time and volume of water consumed.

Dosing:

- Apramycin, 30 mg per kg of body weight, will be infused IV (in a vein) in a volume of 30 mL (1 oz, 2 tablespoons) over 30 minutes using a syringe or infusion pump.
- Report any side effects that you may experience.
- Document your use of any medications.
- Physical exam may be done as needed depending on your symptoms.

After Dosing, the following procedures and assessments will be performed:

Safety procedures:

- Report any side effects that you may experience.
- Document your use of any medications.
- Physical exam may be done as needed depending on your symptoms.
- 12-lead ECG (standard) approximately 1, 4, and 16 hours after dosing.
- Vitals signs (blood pressure, heart rate, breathing rate, oral temperature) measured approximately 1, 4 and 16 hours after dosing and as needed.
- Blood drawn to measure the concentration of study drug approximately at 0.5, 1, 2, 4, 8 and 16 hours after dosing.
- The infusion site will be checked at 1 hour and 16 hours after the infusion and as needed because of symptoms that you might have.
- You will not have food to eat until approximately 2 hours after dosing unless you are scheduled to have a bronchoscopy on this day (Day 1). In that case, you will not have solid food at least 4 hours before the procedure and start eating after you recover and are able to swallow. You will receive liquids before the procedure and as soon as you can swallow after the procedure.
- You will continue drinking water until 24 hours after he infusion. Document time and volume of water consumed.
- You should avoid strenuous physical exercise and exposure to loud noises after dosing and until the study end.

Bronchoscopy with Bronchoalveolar Lavage (BAL):

- Bronchoscopy with Bronchoalveolar lavage will be done only once after dosing on Day 1 if you were assigned to study treatment groups T1–T4.
- You will be accompanied by study staff to the bronchoscopy procedure.
- The procedure will be explained to you. The entire procedure, including prep and recovery time, typically takes about four hours. Bronchoscopy itself usually lasts about 30 to 60 minutes.
- Safety monitoring will be initiated by bronchoscopy staff. Your vital signs (blood pressure, heart rate, respiratory rate) and ECG will be monitored continuously from before the procedure to the time you have fully recovered.
- Your blood oxygen will be monitored continuously with a pulse oximeter, a small probe attached like a clamp to one of your fingers.

- An intravenous catheter, if not already in place, will be inserted in one of your hand or forearm veins to provide IV fluids, and medication as needed.
- You may receive oxygen through a nasal canula as needed.
- You will be given a sedative or light anesthesia by vein. You will be told what drug will be used.
- The bronchoscopist will perform the bronchoscopy and collect bronchoalveolar lavage (BAL) samples.
    - A flexible bronchoscope (a thin instrument, having the width of a pencil, with several channels that allow to see inside the lung and inject and/or remove fluid) will be inserted through your nose or mouth, and then past your vocal cords into the bronchus (large airpipe) of only a lobe (a segment) of your lung. A local anesthetic will be given as the bronchoscope passes through your airway.
    - Lavage will be done with sterile sodium chloride (salty water for injection). While the bronchoscopist ensures that the tip of the bronchoscope is in the selected lung lobe, an assistant will inject into the lung lobe a measured volume, about 50 mL (about 1.7 ounces or 3 tablespoons), of sterile sodium chloride with a syringe through one channel of the bronchoscope and then aspirate it (remove it) with gentle suction with the same syringe. The same lavage will be repeated 3 more times.
    - The procedure ends when the bronchoscopist removes the bronchoscope from your lung and airways.
- You will then be transferred to the recovery room.
    - Your vital signs, ECG and oxygen will be monitored continuously.
    - You may receive oxygen through a nasal cannula as needed
    - You will receive medication as needed.
    - Study staff may perform additional assessments according to the study plan, such as take blood for analysis of the study drug or record an ECG, while you are in the bronchoscopy suite or recovery room.
    - You will be given fluids to drink as you tolerate.
    - You will be discharged from the recovery room when you are stable and return to the Research Site accompanied by study staff.
- Your monitoring will continue in the Research Site according to instructions by the pulmonologist (lung doctor) who did the bronchoscopy.
    - Your vital signs and oxygen will continue to be monitored frequently.
    - You will receive oxygen and medication as needed.
    - You will continue drinking water (about 2 liters) for 24 hours after dosing. Document time and volume of water consumed.
    - You will eat solid food when you are able to swallow well approximately 4 hours after the procedure.

<u>DAY 2: Inpatient Follow-up</u>

If you were assigned to study treatment group T5 (24 hours):

- You will have bronchoscopy with BAL at 24 after dosing and be monitored as described above for subjects in Groups 1-4 on Day 1.

For all subjects:

- 12-lead standard ECG with 10-second rhythm strip taken at 24 hours and 36 hours after dosing.
- Vital signs measured at 24 hours and 36 hours.
- Blood drawn to measure the concentration of study drug at 24 hours and 36 hours.
- Blood and urine samples collected for clinical laboratory tests.
- Infusion site examined at 24 hours and 36 hours.
- Report any side effects that you may experience.
- Physical exam may be done as needed depending on your symptoms.
- Document medications taken.
- Drink at least 2 L water daily – Document time and volume of water consumed.
- Counsel on avoidance of vigorous exercise and exposure to loud noises.

DAY 3: Inpatient Follow-up

- 12-lead standard ECG with 10-second rhythm strip at 48 hours and 60 hours after dosing.
- Vital signs measured at 48 hours and 60 hours.
- Blood drawn to measure the concentration of study drug at 48 hours and 60 hours.
- Blood and urine samples collected for clinical laboratory tests.
- Infusion site examined at 48 hours and 60 hours after dosing.
- Report any side effects that you may experience.
- Document medications taken.
- Have a physical examination.
- Repeat ear exam and hearing tests.
- Ear otoscopy.
- Audiometry.
- Distortion product otoacoustic emissions (DPOAE).
- You will be discharged from the Research Site after review of clinical laboratory tests, ECGs, and other assessments by PI or authorized clinician and audiologist.
- Note: If the time of discharge is late in the evening, due to delays in starting procedures on Day 1 or personal reasons (such as distance from residence), you may stay in the Research Site overnight and be discharged the following morning.
- Counsel on the avoidance of pregnancy, use of contraception, avoidance of prohibited medication, alcohol, coffee, or caffeinated drinks (not more than 3 cups daily), and recreational drugs.
- If you are male, you will be counseled to avoid sperm donation for 30 days after dosing.
- Counsel on avoidance of vigorous exercise and exposure to loud noises.
- Instruct on the next scheduled visit.

OUTPATIENT FOLLOW-UP PERIOD (Days 4 to 30)

- You will be provided contact information and instructions to report to the Research Site any side effects or new symptoms that you develop during these periods and any medication that you take.

- You will be given appointments to return to the Research Site to have follow-up tests on Day 14 and Day 30 after dosing:

DAY 14 Follow-up

- Obtain 12-lead standard ECG with 10-second rhythm strip.
- Vital Signs measured.
- Weight taken.
- Blood and urine samples collected for clinical laboratory tests.
- Repeat ear exam and hearing tests.
- Ear microscopy.
- Audiometry.
    - Distortion product otoacoustic emissions (DPOAE).
- Infusion site checked.
- Report any side effects that you may experience.
- Document medications taken.
- Have a physical examination.
- Counsel on the avoidance of pregnancy, use of contraception, avoidance of prohibited medication, alcohol, coffee, or caffeinated drinks (not more than 3 cups daily), and recreational drugs.
- If you are male, you will be counseled to avoid sperm donation for 30 days after dosing.
- Counsel on avoidance of vigorous exercise and exposure to loud noises.
- Instruct on the next scheduled visit.

DAY 30– FINAL VISIT (Discharge Visit)

- Report any side effects that you may experience.
- Physical exam may be done as needed depending on your symptoms.
- Document medications taken.
- Blood and urine samples collected for clinical laboratory tests.
- Repeat ear exam and hearing tests.
    - Ear microscopy.
    - Audiometry.
    - Distortion product otoacoustic emissions (DPOAE).
- You will be told if your study participation has completed.
- If you have any side effects that need further follow up, you will be told when to return to the Research Site.

EARLY TERMINATION

If you withdraw or are terminated by the study doctor before you complete the study, you will have the following tests and procedures:

- Vital signs measured.
- Have a physical examination.
- Check infusion site.
- Weight taken.

- Report any side effects that you may experience.
- Document medications taken.
- Obtain 12-lead standard ECG with 10-second rhythm strip.
- Blood and urine samples collected for clinical laboratory tests.
- Obtain blood for measuring the concentration of the study drug (if your early termination occurs within 24 hour of dosing).
- Have ear exam and hearing tests.
- You will be counseled to avoid pregnancy and use contraception for 30 days after dosing.
- If you are male, you will be counseled to avoid sperm donation for 30 days after dosing.

UNSCHEDULED VISIT (if needed)
You may return to the Research Site for an unscheduled visit at any time after your discharge on Day 3 if you have any symptoms that you want to discuss or because the study staff asked you to come in for an evaluation. The following activities at a minimum will be performed:

- Collect information on the side-effects you may experience.
- Document medication taken.
- Vital signs measured.
- Have a physical examination, as needed.
- Have a 12-lead ECG as needed.
- Obtain blood and/or urine for clinical laboratory tests, if applicable.
- Have ear exam and hearing tests, as needed.
- The study staff will give you information and tell you if you need to return for follow up before you next scheduled visit.

BLOOD SAMPLES

Blood samples will be drawn by single needle-sticks or through an IV catheter, as determined by the study staff. An IV catheter is a small plastic tube inserted into your arm vein by a needle. The needle is removed, but the tube temporarily remains in your vein. This tube allows the removal of blood without having to stick you each time. The total amount of blood drawn will be up to about 188.5 mL (about -6.5 oz) during the in-patient study treatment period (Days 1 to Day 3) and 262.1 mL (about 8.7 oz or less than a cup of water) during the entire study (from screening to the final visit on Day 30). For comparison, a standard blood donation at a blood collection center, once in a 56-day period, is about 500 mL (2 cups) of blood.

Additional blood samples may be drawn during the study, if the study staff considers it necessary for monitoring your health.

Blood samples and collected data will only be used for this study. Blood samples left after all routine clinical laboratory testing is done will be discarded by the clinical safety laboratory.

YOUR ROLE IN THIS STUDY:

Taking part in a research study can be an inconvenience to your daily life. Please consider the study time commitments and responsibilities as a research subject when you are deciding to participate. Your responsibilities as a subject include the following:

- You cannot participate in this study if you have participated in a prior study within the past 30 days. You must agree that under no circumstance will you take another investigational drug during this study, because it may cause serious physical harm or death and result in permanent restriction for any future studies.
- You must provide accurate responses to questions about your past medical and surgical history (illnesses and surgeries you had including abnormal lab tests, X-rays, and other procedures), medications you are taking, medications you are allergic to and your family history. Failure to respond accurately may result in side-effects that may be harmful after you receive the study drug or have during and after bronchoscopy with alveolar lavage (BAL).
- You must read, and agree to follow, the House Rules at the Research Site if you want to take part in this study. House Rules discuss proper behavior at the Research Site and are important to ensure your safety and make sure the study results are accurate. Failure to follow these rules may result in reduced compensation or involuntary discharge from this study.
- You must report any side effects and medical problems to the study staff.
- You must give true and complete answers to any questions.
- You must be able to comply with the study procedures and visit schedule.
- You must follow all instructions from the study staff.
- You must inform the study staff if you decide to discontinue your participation in the study. If you decide to discontinue your participation in the study, you may be asked to consent to stay in the study and complete any remaining procedures for the most recent study treatment period. If you do not consent to complete any remaining procedures, you will be asked to complete the early termination visit procedures as described in this consent form.
- You must agree to use an effective method of contraception, as defined later in this consent form, throughout the study. If you are male, you must agree not to donate sperm for 30 days after dosing.
- You must not do any vigorous activity for 2 days before the dosing until discharge from the Research Site on Day 3, and for 24 hours before each out-patient follow up visit on Day 14 and Day 30. Or at any time during the study.
- You must avoid exposure to loud noises (for example, construction sites, visiting concerts or dance events, fireworks, listening to music with headphones) from screening until Day 30 (final visit).
- You must not consume alcohol for 2 days before check-in on Day -2 until your discharge from the Research Site on Day 3, and it is recommended to avoid alcohol during the out-patient follow-up until Day 30 (final visit). *Tell the study doctor if you consumed any alcoholic beverages during this time.*
- You must not use marijuana or other illegal drugs during the study.
- You must not drink liquids or eat foods that contain caffeine within 2 days before dosing and during the inpatient study treatment period, and no more than 3 cups of coffee or caffeine-containing drinks during the out-patient follow-up period to the end of the study. *Tell the study doctor if you consumed any coffee or caffeine-containing beverages during this time.*

- You will be advised to avoid smoking after screening. Smoking is prohibited during the in-patient period of the study (Day -2 to Day 3) and recommended to avoid smoking during the follow-up out-patient period to the end of the study (Day 4 to Day 30). *Tell the study doctor if you consumed any coffee or caffeine-containing beverages during this time.*
- You must not participate in another research study at any time during this study or continue participating in another study and have blood draws. This includes studies of a drug, biologic (such as vaccine or proteins), device, or blood product.

PROHIBITED MEDICATIONS, VACCINATIONS, and BLOOD DONATIONS:

Additional restrictions to ensure the health and safety of study subjects are listed below:

- You must not take any prescription medications within 30 days before dosing or during the study. Certain drugs should be avoided for a longer period before taking the study drug. (See Risks of Apramycin below)
- You will continue taking birth control medications that you were already using. Certain other medications may be permitted if approved by the study staff. *Please report all prescription medications you are taking*.
- You must not take any non-prescription medications, herbs, vitamins, or nutritional supplements from the time of screening (about 28 days before dosing) to 14 days after dosing, with the exception of single doses of acetaminophen up to 1,000 mg. Certain non-prescription medications are prohibited if taken 15 days before dosing, and others may be permitted if approved by the study staff. *Please report all non-prescription medications, herbs, vitamins, or nutritional supplements you are taking.*
- You must not donate any blood or blood products (red cells, white cells, platelets, plasma) during the course of this study. Tell the study doctor if you donated any blood or blood products within 3 months before dosing.
- You must not receive any blood or blood products during this study.

RISKS of APRAMYCIN:

Observed risks:

There were no identified risks associated with apramycin in the completed first in human study in 30 healthy subjects who were given IV single apramycin doses ranging from 0.3 to 30 mg/kg body weight. One subject had decreased hearing at one test after dosing but not on a repeat and the effect was not considered related to the study drug. Apramycin was safe and well-tolerated and there were no clinically important changes in laboratory tests and ECGs during that study.

Potential Risks:

Until more clinical experience with apramycin is available, similar undesirable effects as observed for other aminoglycosides should be anticipated. Special attention will be paid to signs and symptoms of kidney injury, hearing loss and balance disorders.

Based on the knowledge on other aminoglycosides, the following contraindications to the use of apramycin will be assumed until further testing, because of potentially higher risk if you have a history of the following:

- Hypersensitivity or an allergic reaction to aminoglycosides.

- Myasthenia gravis (a chronic autoimmune, neuromuscular disease that causes weakness in the skeletal muscles that worsens after periods of activity and improves after periods of rest).
- Kidney failure.
- Hearing loss.
- Balance problems, especially those caused by a disorder of the inner ear (for example, Meniere's disease), vertigo (a sensation of dizziness and loss of balance, with a feeling like you are spinning or that the world around you is spinning), ataxia (impaired coordination of movement).

Potential Drug Interactions:
There are no clinical data on drug interactions with apramycin. However, based on the knowledge about other aminoglycosides, concomitant administration of the following drugs should be avoided for the indicated period before dosing to the end of the study:

- Drugs affecting kidney function for 2 weeks before dosing with apramycin: blood pressure and medications for heat failure (such as enalapril, lisinopril, ramipril captopril, benazepril), spironolactone, and epleronone); and anti-inflammatory drugs (such as aspirin, ibuprofen, naproxen, indomethacin, bextra, celebrex, vioxx).
- Drugs with potential ear toxicity and permanent hearing loss for 3 months before dosing with apramycin: vancomycin, loop diuretics (bumetanide [bumex], ethacrynic acid (edecrin), furosemide [Lasix]), quinine and quinidine derivatives including mefloquine.
- Neuromuscular blocking agents (drugs that block the transmission of nerve signals to the muscles and cause muscle paralysis) within a week before dosing: tracrium, norcuron, pavulon, and others.
- Other aminoglycoside antibiotics within 3 months before dosing with study drug: gentamicin, tobramycin, kanamycin, streptomycin, neomycin.

Allergic Reaction Risks
As with taking any drug, there is a risk of allergic reaction. If you have a very serious allergic reaction, you may be at risk of death. Some symptoms of allergic reactions are:

- Rash
- Wheezing and difficulty breathing
- Dizziness and fainting
- Swelling around the mouth, throat or eyes
- A fast pulse
- Sweating

Please seek treatment immediately and tell the study doctor and study staff if you have any of these symptoms.

Use During Pregnancy and Lactation:
Aminoglycosides pass the placenta barrier and may cause fetal harm. Therefore, you should not participate in the study if you are pregnant or plan to become pregnant during the study.

Aminoglycosides have been reported to be detected in maternal milk. Therefore, you should not participate in the study if you are breastfeeding.

Overdose
There is no specific antidote in case of apramycin overdose. The same measures as recommended for other aminoglycosides (treatment cessation, adequate hydration, dialysis) will be considered until clinical data are available for apramycin.

Drug Abuse and Dependency
No clinical experience available.

RISKS OF BRONCHOSCOPY WITH BRONCHOALVEOLAR LAVAGE:
Bronchoscopy with bronchoalveolar lavage has a proven safety record in both clinical applications as well as human research during more than 40 years of clinical use of this procedure in hundreds of thousands of subjects, without any serious lung troubles and side effects. However, like all procedures, there are some risks associate with it.

The most common side effect related to the procedure is transient hypoxemia (drop in oxygen content in the blood), which may require administration of oxygen. Transient tachycardia (increased heart rate) and premature contractions, which may require no treatment or appropriate intervention.

Other side effects that could occur are nausea and dizziness, due to the drugs used for sedation or anesthesia, and nasal stuffiness and irritation, throat irritation, hoarseness and cough, due to the passage of the bronchoscope and the bronchoalveolar lavage (BAL; instilling saline into a lung segment (lobe).

A post-bronchoscopy fever (PBF), usually less than 40˚C / 100°F may occur. The incidence varies from 0% in large series to up to 10% reports in smaller series. It may occur about 8 hours after BAL and lasts about 14 hours. It is not accompanied by bacterial infection or pneumonia with abnormal chest X-ray, and it could be a rare natural reaction to the procedure. Antibiotics are not used for prevention and treatment targets the symptoms (drugs to lower fever, good hydration). Additional tests may be needed to guide treatment.

Rare complications, with incidence 0.1 to 0.3%, are perforation of the bronchus with pneumothorax (collection of air in the chest cavity), and atelectasis (collapse of the segment of the lung where the bronchoscope is inserted), and infection. Bleeding has been described for bronchoscopy with biopsy of the lung but is very rare (0.1% or less) if only bronchoalveolar lavage is done. These are related to mechanical trauma, especially in subjects who have a disorder of blood coagulation or take anticoagulants (heparin, warfarin, new anticoagulants) and non-prescription non-steroidal anti-inflammatory drug (such as aspirin, and ibuprofen).

These risks are mitigated by adherence to the study plan. As mentioned above, you are expected to provide accurate and truthful information about past and current illnesses and use of medications. You are going to have a thorough physical examination and clinical lab testing to

exclude any abnormalities that are contraindications to receiving the study drug and having the procedure. Finally, the procedure is performed by experienced pulmonary physicians (lung specialists) that are certified to perform this procedure, assisted by experienced and certified personnel in specially equipped hospital rooms equipped to handle emergencies.

RISKS OF AUDIOLOGY TESTS:
There are no risks associated with the planned procedures to examine your ears and hearing. The procedure will be performed by experienced and certified audiologists.

BLOOD SAMPLE RISKS:
There may be side effects of drawing blood with a needle and/or IV tubes and IV catheter placement. Local pain, bruising, bleeding, inflammation or infection might occur at the site of the needle stick where blood is drawn. There is a possibility of dizziness or fainting while your blood is being drawn. Precautions will be taken to minimize the above complications. There is a small risk your blood counts will decrease slightly during the course of the study, but not expected to cause anemia (low blood counts that cause symptoms and need treatment). Any symptoms that may occur are usually reversible with good nutrition, drinking fluids, vitamins, and iron.

ECG RISKS:
ECG patched may case a skin reaction such as redness or itching. You may also experience localized skin discomforts and/or hair loss associated with the placement of ECG patches.

UNKNOWN RISKS:
You may have side effects or discomforts that are not listed in this form. Some side effects may not be known yet. New ones could happen to you. Tell the study staff right away if you have any problems.

INFORMATION ON BIRTH CONTROL:

Females:
The effect of apramycin on the unborn child is unknown at this time. Therefore, it is important that women who are pregnant, may become pregnant or who are breastfeeding NOT participate in this study. If you are a woman who can get pregnant, you must use an acceptable form of birth control that is very effective in preventing pregnancy. You must agree to use birth control for at least 30 days after dosing. You agree to avoid becoming pregnant during this study.

The following are acceptable forms of birth control for this study:

- Progestin implants.
- Intrauterine devices (IUD).
- Surgery to prevent pregnancy in females (such as bilateral tubal ligation/occlusion, salpingectomy [removal of the tubes], oophorectomy [removal of the ovaries], or hysterectomy [removal of the uterus]).
- Abstinence.

Tell the study staff if you use any other forms of birth control.

If at any time during this study you think you may be pregnant, you are required to immediately contact the study doctor at the telephone number on the first page of this form.

Males:
The effect of apramycin on the unborn child is unknown at this time. The effect of the study drug on the male reproductive system is unknown. Therefore, you must agree to use an acceptable form of birth control from dosing with study drug through at least 30 days after dosing. Acceptable birth control means not having sex (abstinence) or having a vasectomy. If you are sexually active, you should agree to use a condom throughout this study and for at least 30 days after dosing. **Tell the study staff if you use any other form of birth control.**

You should also not donate sperm for 30 days after dosing.

It is also recommended that you make certain that your female partner is also using an acceptable form of birth control if you have not had a vasectomy and are using a condom. If you think that your partner may be pregnant at any time during this study to 30 days after dosing, you are required to immediately contact the study doctor at the telephone number on the first page of this form.

REPORTING PREGNANCY:
If you are a woman, you should report to the study staff if you miss your period and suspect you are pregnant or if you become pregnant during the 30 days after dosing. With your permission, blood samples will be collected, and you will continue to be followed for safety during this study. You should provide pregnancy outcome to the study staff upon delivery or pregnancy termination.

If you are a male and your female partner becomes pregnant during the 30 days after dosing, you should inform study staff of the pregnancy and provide pregnancy outcome upon delivery or pregnancy termination.

INFORMATION ON USE OF ALCOHOL, MARIJUANA OR OTHER ILLEGAL DRUGS:
You are not allowed to use alcohol, marijuana or other illegal drugs (such as cocaine, etc.), because they may cause you serious harm and are strictly forbidden while you are in this study. You will be tested for drugs and alcohol at Screening, and on Day -2. If you are found to be in possession of or using marijuana or other illegal drugs at the Research Site, then AMR-Knoxville is obligated to report the use of marijuana or other illegal drugs to the appropriate legal authorities.

INFORMATION ON ACTIVITIES TO AVOID:
You should avoid vigorous exercise from at least 2 days before your admission to the Research Site to after the discharge on Day 3 after dosing and 24 hours before each follow-up visit (Day 14 and Day 30).

You should avoid exposure to loud sounds (listening to music or playing videogames with headphones on, attending indoor concerts and other entertainment venues, etc.) from signing and dating informed consent until Final Visit (Day 30).

NEW INFORMATION ABOUT APRAMYCIN:
The study doctor or study staff will discuss with you any important new information, findings or changes to the way the research will be performed that may affect your decision to remain in this study. If this happens, you will be asked to decide if you want to keep taking part in this study. You may be given an additional informed consent and will be asked to agree in writing that you were told about these new findings.

BENEFITS TO THE STUDY SUBJECT:
The goal of this research study is to provide scientific information. You will not receive any medical benefits. This study may help doctors and scientists learn things about the study drug that will help others.

ALTERNATE THERAPY:
This is a clinical research study. It is not treatment or therapy. The other choice is to not participate in this study.

PAYMENT FOR PARTICIPATION:
If, after screening, you are enrolled in the study and complete all of the study visits, you will receive a total of up to $4,050.00 at your completion of the study to help cover the costs of your participation and compensate you for your time. If, after screening, it is determined that you qualify to be enrolled in the study, but you choose not to enroll, you will not be compensated for completing the screening process. Compensation will be made at the following intervals:

- Completion of Day 3 at: $2,000.00
- Completion of Day 30/End of Study at: $2,050.00

If after enrollment, your participation is ended early, or if you withdraw for any reason, the amount you will be paid will be prorated and the payment made when you complete your participation in the study. This means that you will receive payment only for the portion of the study that you completed and only after your participation in the study has been completed. Payment will be prorated as follows:

Visit 1	Screening	$400.00
Visit 2	Check-in, Day -2	$425.00
	Baseline, Day-1 Baseline	$425.00
	Study Treatment Period, Day 1, Dosing	$1,500.00
	Study Treatment Period, Day 2, In-patient Follow up	$425.00
	Study Treatment Period, Day 3, In-patient Follow-up / Discharge	$425.00
Visit 3	Outpatient Follow Up Period, Day 14	$150.00

Visit 4	Outpatient Follow Up Period, Day 30 (Final Visit)	$300.00
	Total	$4,050.00

Compensation for participation in the study will be made using a reusable, pre-loaded card (similar to a debit card). You must not lose the card during your participation in the study. If the card is lost, stolen, or destroyed, you will be charged a $5.00 fee to issue a replacement card.

If you test positive for illegal drugs at any time during the study, you will be withdrawn from the study and not be given any amount of compensation.

If you have any questions regarding your compensation for participation, please contact the study doctor at the telephone number listed on page one of this consent document.

If, after enrollment, your participation is terminated or you decide to withdraw for any reason, you will be compensated $150.00 for completing the early termination/withdrawal visit procedures. If you have an unscheduled visit, you will be compensated $100.00 for completing the unscheduled visit procedures.

In addition, you will be advised of, and asked to sign and date a document entitled "Research Site Guidelines". These rules outline penalties for certain violations of our rules for when you are staying at the clinic. Violations, should they occur, may result in reduction of the compensation described above.

If the amount of compensation from your participation is over a certain amount, the law requires Alliance for Multispecialty Research, LLC to report the compensation you receive to the Internal Revenue Service. No deductions from your compensation for taxes will be made by Alliance for Multispecialty Research, LLC. It is your responsibility to report this compensation on your federal tax returns and to pay any taxes that are due.

COMPENSATION FOR INJURY:

- In the event that you experience an adverse reaction (side-effect), illness or injury during this study, you should immediately seek treatment. It is important that you tell your study doctor if you have experienced one of these events. You must contact the study staff at the telephone number on the first page of this form as soon as you are able. You may obtain medical care in the same way as you would ordinarily receive any other medical treatment. Immediate necessary care, emergency treatment, and professional services will be available to research subjects just as they are to the community generally. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH or the Federal Government.
- Medical care will be given to you, at no cost, if you are injured because of being in this study.

- While you are in this study, you may be injured because of your personal conduct or during activities, which are not part of this study. There are no plans to pay you for these types of injuries.

COSTS TO YOU:
There is no cost to you to participate in this study. You do not have to pay for any study-related drugs, procedures, or treatment at the Research Site during this study.

SOURCE OF FUNDING:
This research study is being funded by NIAID, which has a contract with a company named DVC to do studies like this one. AMR-Knoxville has signed and dated a contract with IQVIA, Inc., a subcontractor of DVC, to conduct this research study under the direction of the study doctor.

VOLUNTARY PARTICIPATION IN THIS STUDY:
Your participation in this study is voluntary. You will be starting this study of your own free will and without any kind of pressure. You may quit this study any time you wish. If you withdraw from this study, you will not be penalized. You will not lose any benefits to which you were otherwise entitled.

If you have health problems, you will get medical attention. You may be withdrawn from this study by the study staff and/or the sponsor of this study, without your consent, if it is in your best medical interest. It is possible that the study staff and/or sponsor may think you can stay in this study. You must decide what you want to do.

The study staff or the sponsor may stop your participation in this study at any time without your consent for any of the following reasons:

- If you don't follow the study staff's instructions;
- Something serious happens to you which may require treatment;
- The study staff decides it is in the best interest of your health, and welfare to discontinue further participation;
- The sponsor stops this study for other reasons not known now;
- You do not later consent to any future changes that may be made in the study plan; or
- For any other reason.

If you received any amount of the study drug but withdraw from the trial within 24 hours after dosing, you will be encouraged to continue follow-up (with your consent) for safety assessments and PK sample collection.

The FDA, the Safety Monitoring Committee (SMC), and Advarra IRB may also terminate this study if there are safety concerns.

If you do not complete this study for any reason, you will be asked to undergo a physical exam, vital signs measurement, 12-lead ECG, blood and urine laboratory tests, a pregnancy test (females

only), ear and hearing tests and tests for the measurement of apramycin in your blood if early termination occurs within 24 hours of dosing. This is needed to identify any changes that may have occurred after you began to take the study drug and to protect your safety, health, and welfare.

CERTIFICATE OF CONFIDENTIALITY:

To help us protect your privacy, we have a Certificate of Confidentiality from NIH. The study staff can use this Certificate to legally refuse to give information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The study staff will use the Certificate to resist any demands for information that would identify you, except for reporting of communicable diseases, such as Hepatitis Virus and HIV infections, to state and local health departments, or for reporting possession or use of marijuana or other illegal drugs while at the Research Site to the appropriate legal authorities.

A Certificate of Confidentiality does not prevent disclosure of your information to the NIH, FDA, or federal funding agency. Information from this study will be given to DMID and Juvabis AG, the pharmaceutical organization developing apramycin and other drugs for the treatment of infectious diseases. Any persons or companies, which are contracted by the sponsor for conducting this study, measuring drug level in blood samples, monitoring the execution of this study, and analyzing the data, will have access to the research information during and after this study.

The information will also be given to the FDA. It may be given to governmental agencies in other countries where the study drug may be considered for approval.

Authorization to Use and Disclose Protected Health Information

If you decide to be in this study, the study doctor and study staff will use and share health data about you to conduct the study. Health data may include:

- Your name.
- Address.
- Phone number.
- Date of birth.
- Medical history.
- Information from your study visits, including all test results.

Health data may come from your study records or from existing records kept by your doctor or other health care workers.

Medical records which identify you and the consent form signed and dated by you will be looked at and/or copied for research or regulatory purposes by:

- The sponsor;
- An agent for the sponsor;

- An agent for the study doctor;
- The FDA;
- Department of Health and Human Services (DHHS) agencies; and
- The Institutional Review Board, Advarra IRB.

Your health data will be used to conduct and oversee the research, including for instance:

- To see if the study drug works and is safe.
- For other research activities related to the study drug

Absolute confidentiality cannot be guaranteed because of the need to give information to these parties. The results of this research study may be presented at meetings or in publications. Your identity will not be disclosed in those presentations.

- AMR-Knoxville will handle the medical information obtained in this study with the strictest confidence. It will be protected as required by laws and/or regulations. It will not be made publicly available.
- If the results of this study are published, you will not be identified by name.
- Your identity will not be disclosed to anyone else, unless required by law.

By signing and dating this consent, you authorize AMR-Knoxville to verify your study participation history with other businesses that conduct clinical research studies.

A Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If you give your consent to release information to a medical care provider, an insurer, or other person to receive research information, then the researchers will not withhold that information.

Your permission to use and share health data about you will end in 50 years unless you revoke it (take it back) sooner.

You may revoke (take back) your permission to use and share health data about you at any time by writing to the study doctor at the address listed on the first page of this form. If you do this, you will not be able to stay in this study. No new health data that identifies you will be gathered after your written request is received. However, health data about you that has already been gathered may still be used and given to others as described in this form.

Your right to access your health data in the study records will be suspended during the study to keep from changing the study results. When the study is over, you can access your study health data.

If you decide not to sign and date this form, you will not be able to take part in the study.

PRIMARY CARE PROVIDER NOTIFICATION

We would like your permission to contact the primary care provider you see regularly to let them know that you are taking part in this study. It is important for all your healthcare providers to

know that you may be taking an experimental drug. Your healthcare provider will want to know and think about all the drugs you are taking before giving you any new ones. While you are in the study, the study doctor will ask about your symptoms. If you have symptoms after the study ends, your primary care provider may want to contact the study personnel.

If you agree, your primary care provider (regular provider) will be informed of your participation in the study. Indicate your choice below by initialing only one (1) section below.

_____ Initials	I do not have a primary care provider.
_____ Initials	I do not want my primary care provider notified.
_____ Initials	I would like my primary care provider notified and below is my physician's contact information.

FUTURE USE OF RESIDUAL PLASMA AND BRONCHOALVEOLAR LAVAGE (BAL) SPECIMENS

We would like to ask your permission to store any residual (left-over) blood (plasma) and bronchoalveolar lavage fluid collected for measuring the concentration of apramycin for use in future studies. You can choose whether to allow residual collections of blood (plasma) and BAL fluid to be stored for future use or destroyed at the end of your participation in the study.

These samples will be stored in test tubes labeled with a code number without information which could identify you. It does not identify you by name or provide any other personal information that can lead to your identification by someone who does not have access to the code (see Section on Confidentiality of Records). The code number on the test tube label is used to track the day and time of plasma or BAL fluid collection and your assigned study number. All stored samples will be used only for related research purposes. The samples will not be sold or used directly for production of any commercial product. Human genetic (DNA) tests will not be performed on these blood samples. Blood and BAL fluid samples obtained in this study may result in the development of a product that could be patented or licensed. There are no plans to provide financial compensation to you should this occur.

Your decision may be changed at any time by notifying the study doctor at the telephone number on the first page of this form. You will be asked to sign and date a new form to demonstrate your new decision. Your decision regarding these specimens will not affect your participation in this study or other studies.

If you agree/disagree to your blood and BAL fluid specimens being stored for future studies, please initial and date your choice below.

_____ (initial) (date)	**YES**, you may store my unused blood (plasma) and BAL fluid samples in coded tubes samples for an indefinite period of time for future research without removing the link to my personal identifying information.
_____ (initial) (date)	**YES**, you may store my unused blood (plasma) and BAL fluid samples in coded tubes samples for an indefinite period of time only after removing the link to my personal identifying information.
_____ (initial) (date)	**NO**, you may not store my unused blood (plasma) or BAL future samples for future research. Destroy all unused samples at the end of the study.

WHOM TO CONTACT ABOUT THIS STUDY
During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the study doctor at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects. If you have any questions about your rights as a research subject, and/or concerns or complaints regarding this research study, contact:

- By mail:
  Study Subject Adviser
  Advarra IRB
  6100 Merriweather Dr., Suite 600
  Columbia, MD 21044
- or call **toll free**: 877-992-4724
- or by **email**: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: **Pro00059918**.

CONSENT and AUTHORIZATION

I have read all information in this document, and all my questions have been answered to my satisfaction. I voluntarily consent to participate in this study. I will be given a signed and dated copy of this consent form and have been told the description of the study drug, and the name, address and phone number of the study doctor. My signature and date give my consent to participate. I authorize the release of my medical records and health information related to this study, including my signed and dated consent form and any addendum, to the sponsor and its representatives, the FDA, Advarra IRB and other regulatory agencies as described above. By signing and dating this form, I have not given up any of my legal rights as a research subject.

Printed Volunteer's Name	Date
Volunteer's Signature	
Person Obtaining Informed Consent Printed Name	
Person Obtaining Informed Consent Signature	Date
Witness Printed Name	
Witness Signature	Date
Investigator's Signature*	Date

*The Investigator's signature evidences only that the Investigator has reviewed the consent form and the signatures and dates of the subject, person obtaining consent, and witness, for compliance.